(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/68655 A2

(51) International Patent Classification[7]: C07F 9/02

(21) International Application Number: PCT/US01/07935

(22) International Filing Date: 12 March 2001 (12.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/523,243 10 March 2000 (10.03.2000) US

(71) Applicant *(for all designated States except US)*: **ARIAD PHARMACEUTICALS, INC.** [US/US]; 26 Landsdowne Street, Cambridge, MA 02139-4234 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DEPREZ, Pierre** [FR/FR]; 4, rue Albert de Dion, F-94320 Thiais (FR). **LESUISSE, Dominique** [FR/FR]; 11, rue des Federes, F-93100 Montreuil (FR). **BENARD, Didier** [FR/FR]; 4, allée du Parc, F-95570 Attainville (FR).

(74) Agent: **BERSTEIN, David, L.**; Ariad Pharmaceuticals, Inc., 26 Landsdowne Street, Cambridge, MA 02139-4234 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA.

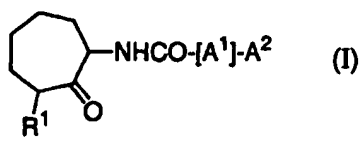
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/68655 A2

(54) Title: CAPROLACTAM DERIVATIVES AND USES THEREOF



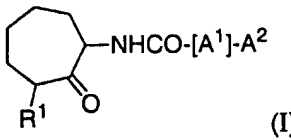
(I)

(57) Abstract: The invention involves derivatives of caprolactam of the formula (I) in which [A^1], A^2 and R^1 have the meanings indicated in the description, their salts and their prodrugs. The invention also relates to the preparation of such compounds, synthetic intermediates, their use, and in particular, antagonists of the Src SH2 domain and inhibitors of bone resorption and pharmaceutical compounds containing such compounds.

Caprolactam Derivatives and Uses Thereof

This invention relates to new caprolactam derivatives, their preparation, synthetic intermediates for their synthesis, their uses and pharmaceutical compositions containing them.

The compounds of this invention include caprolactam derivatives of formula (I) , their physiologically acceptable salts and their prodrugs:



(I)

in which $[A^1]$, A^2 and R^1 have the meanings indicated below. The compounds of particular interest have biological and pharmacological activity and are useful as research tools for the study of Src function and its inhibition and as medications, particularly as antagonists of Src, and as inhibitors of bone resorption, e.g., as mediated by osteoclasts. Such compounds are useful for therapeutic or prophylactic treatments of diseases or conditions mediated by Src, including those involving an undesirable increase in bone resorption, for example osteoporosis. This invention also provides synthetic intermediates and procedures for preparing compounds of formula (I), and pharmaceutical uses and compositions containing them.

Background Information on Tyrosine Kinases

a) Tyrosine kinase catalytic activity

Tyrosine kinase catalytic activity is thought to be associated either with receptors having transmembrane domains (EDF, DPGF, c-fms) or intra-cellular proteins (T. Hunter, Biochem Soc. Trans; 24, 307 - 327 (1996)). The intracellular tyrosine kinases ("non-receptor") are divided into 8 subfamilies mainly according to the sequence similarity in their catalytic domain and have been called by the name of their best known member (Src, Csk, Btk, Abl, Fak, Syk, Jak, Fsp). Within this class of intracellular tyrosine kinases, the Src family contains 9 members sharing among them 70% of the sequence homology (Src, Fyn, Yes, Frg, Lyn, Hck, Lck, Blk, Yrd in the vertebrates).

b) Src family proteins

The proteins of the Src family share a common structure which is characterized by the following elements: a small N-terminal fragment involved in anchoring to the membrane (sometimes also called SH4), a single domain that is not well conserved (40 - 70 residues), an SH3 domain which connects to the sequences that are rich in proline (50 residues), an SH2 domain involved in the recognition of the specific phosphorylated peptide sequence (100 residues), a catalytic domain (tyrosine kinase, 250 residues) and finally a short C-terminal domain involved in regulation.

c) Function of the tyrosine kinase proteins of the c-Src family

The tyrosine kinase proteins of the c-Src family have multiple roles and overlap at the level of signal translation involved in a number of different biological situations, in particular cellular growth and differentiation, control of the cell cycle, of the form and of the adhesion of cells as well as regulation of ion channels and neurotransmitter receptors.

While the expression of the majority of the members of the Src family is limited to the hematopoietic system, the proteins Src, Fyn and Yes are expressed in a large number of tissues and cellular types. The gene c-Src in particular is largely expressed in neurons, platelets and osteoclasts.

d) Bone resorption and c-Src

The biological functions of several of these proteins have finally started to be better understood with the start of the knock-out experiments. Thus, Soriano et al. (Cell 64, 693 - 702 (1991)) recently generated a line of transgenic mice in which the c-Src gene was not functional. Observation of the phenotype of the homozygote mice for this mutation revealed several interesting facts: they did not have obvious abnormality at the level of neurons or platelets, on the other hand these mice were all affected by a very diminished bone resorption which gives rise to skeletal abnormalities (S.N. Popoff et al.; Bone 17(5) 437 - 445). It was then shown that these mice had a normal number of osteoclasts but that the latter did not have any brush edges and were not capable of normal resorption in the pit test (B.F. Boyce et al. J. Clin. Invest. 90, 1622-27 (1992)).

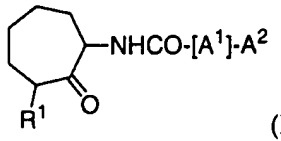
Thus, only the osteoclasts seem to be affected by the mutation. It is therefore possible that in the neurons, platelets and other cells in which Src exercises a function, this function could be carried out by another Src family member (*e.g.*, fyn, lyn or yes); in contrast, this functional substitution would not take place in the osteoclasts.

e) Inhibition of the Src protein

New inhibitors of bone resorption would clearly be desirable, including such agents, as disclosed herein, that function by inhibition of Src.

Further Description of the Invention

The compounds of this invention include caprolactam derivatives of formula (I):



(I)

in which:

-R^1 is either R'^1 or R''^1, where

R'^1 represents an aliphatic or aryl group (which may be substituted or unsubstituted), usually selected from the following: (C_1-C_8)-alkyl-, (C_2-C_8)-alkenyl-, (C_2-C_8)-alkynyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkyl-, (C_5-C_{14})-aryl-(C_2-C_8)-alkenyl-, (C_5-C_{14})-aryl-(C_2-C_8)-alkynyl-, (C_3-C_{18})-cycloalkyl-(C_1-C_8)-alkyl-, (C_3-C_{18})-cycloalkyl-(C_2-C_8)-alkenyl-, (C_3-C_{18})-cycloalkyl-(C_2-C_8)-alkynyl- or (C_5-C_{14})-aryl-, where the alkyl, alkenyl, alkynyl, aryl and cycloalkyl groups are non-substituted or substituted by one or several R^2 radicals; and,

R''^1, represents the following groups:
-CHRa-CO-R'^1, -CHRa-CONH-R'^1, R'^1 being as defined above;

-[A^1]- is a group selected from among: -CH(Z)-(C_1-C_4)-alkyl-(C_5-C_{14})-aryl-, -C(Z)=CH-(C_0-C_2)-alkyl-(C_5-C_{14})-aryl-, -CH(Z)-(C_5-C_{14})-aryl-, -(C_1-C_4)-alkyl-(C_5-C_{14})-aryl- and -(C_5-C_{14})-aryl-, in which Z is an atom of hydrogen, a tetrazole, NRbRc, NHCORb, CONHRb, $NHCO_2Rb$, $NHCOCO_2Rb$, NHSORb or $NHSO_2Rb$; wherein the aryl radicals are non-substituted or substituted with R^2 or R'^2;

- A_2 is a group selected from among: -PO (ORd) (ORe), -OPO (ORd) (ORe), -B (ORd) (ORe), -CRfRgPO (ORd) (ORe), -O-CRfRgPO (ORd) (ORe), -CRfRg-CO_2Rd, -$CRf(CO_2Rd)_2$, -O-CRfRg-CO_2Rd, -O-CRf $(CO_2Rd)_2$, -N $(CRfRg\text{-}CO_2Rd)_2$, -CO_2Rd, -CRfRg-CH_2-CO_2Rd, -$CRfRgSO_3H$, -O-$CRfRgSO_3H$, -OSO_3H, -OSO_2NH_2, -SO_2NH_2, -NHCO-PO (ORd) (ORe), -CO-PO (ORd) (ORe), -OH, –OCORd, -CH (CH_2CO_2Rd) (CH_2CO_2Re), -NHCO-PO (ORd) (ORe) and -CO-PO (ORd) (ORe);

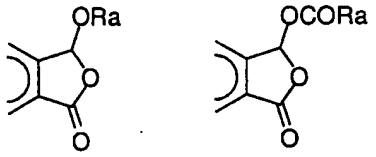
- Ra, Rb, Rc, Rd and Re may be identical to each other or different, being selected independently of each other from the following: H, (C_1-C_8)-alkyl, (C_3-C_{18})-cycloalkyl, (C_3-C_{18})-(C_1-C_8)-alkyl-, (C_5-C_{14})-aryl- and (C_5-C_{14})-aryl-(C_1-C_4)-alkyl-, the foregoing groups being non-substituted or substituted by one or several R^2 radicals;

- Rf and Rg may be identical to each other or different, being selected independently of each other from the following: H, a halogen, a CO_2Rd, SO_3Rd, ORd, NHRd, PO (ORd) (ORe) radical or tetrazole;

- R^2 is a (C_1-C_8)-alkyl-, (C_1-C_8)-alkoxy-, (C_1-C_3)-alkylenedioxy-, (C_5-C_{14})-aryl-, (C_5-C_{14})-aryloxy-, (C_5-C_{14})-aryl-(C_1-C_4)-alkyl-, (C_5-C_{14})-aryl-(C_1-C_4)-alkyloxy-, halogen, trihalogenomethyl-, trihalogenomethyloxy-, hydroxyl, nitro, formyl, -C=NH-NH-CO-NH_2, cyano, carboxy, -$CONH_2$, (C_1-C_8)-alkyloxycarbonyl-, amino, -NH-((C_1-C_4)-alkyl), -N((C_1-C_4)-alkyl)$_2$, -NHCO-(C_1-C_4)-alkyl, -NHCO-(C_5-C_{14})-aryl, -CONH-(C_1-C_4)-alkyl, -CONH-(C_5-C_{14})-aryl, -CO-(C_1-C_4)-alkyl or -CO-(C_5-C_{14})-aryl group;

- R'^2 has the same values as A^2(but independently selected);

- A^2 and R^2 may form, *e.g.* together with a shared phenyl ring, a 5-membered ring as follows:



The compounds of formula (I) may be present in any of their possible isomer forms, alone or in mixtures of any ratio whatsoever, as well as their physiologically acceptable salts and their prodrugs.

Any repeated occurrences of a variable functional group in the compounds of this invention, for example the group R^2, are independent of each other and may be identical or different.

The alkyl radicals (i.e., groups) may be linear or branched, saturated or mono- or polyunsaturated. This also applies when they have a substituent or when they are included in groups such as e.g. alkoxy, alkoxycarbonyl or aralkyl.

Note that the parenthetical expressions such as "(C1-C8)" which may precede a given functional group indicate a numerical range for the number of carbon atoms in that functional group. For example, a "(C1-C8)alkyl group" designates an alkyl group having one to eight carbon atoms and which may contain one or more additional substituents if so indicated. Thus, a (C_1-C_8)-alkyl encompasses methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl groups, including the various isomers thereof, such as n-, i-, t- etc isomers, including by way of example, isopropyl, isobutyl, isopentyl, neopentyl, isohexyl, 3-methylpentyl, 2, 3, 4-trimethylhexyl, sec-butyl, tert-butyl, tert-pentyl. Often preferred alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and tert-butyl.

The bivalent alkylene radicals corresponding to the monovalent radicals mentioned above include, for example, methylene, ethylene, 1, 3-propylene, 1, 2-propylene (= 1-methylethylene), 2, 3-butylene (= 1, 2-dimethylethylene), 1, 4-butylene, or 1, 6-hexylene.

The unsaturated alkyl radicals include, by way of non-limiting example, the (C_2-C_8)-alkenyl radicals such as vinyl, 1-propenyl, allyl, butenyl, 3-methyl-2-butenyl and the (C_2-C_8)-alkynyl radicals such as ethynyl, 1-propynyl or propargyl.

Bivalent alkylene radicals include e.g. alkenylene and alkynylene groups which may also be linear, cyclic or branched, including among others such groups as vinylene, propenylene, ethynylene and propynylene.

The cycloalkyl radicals may be monocyclic, bicyclic or tricyclic. For example, this is a matter of the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, cyclotetradecyl or cyclooctadecyl radicals, which may be unsubstituted or substituted, for example, by an alkyl containing 1 to 4 carbon atoms. Illustrative substituted cycloalkyl radicals include 4-methylcyclo-hexyl and 2, 3-dimethylcyclo-hexyl groups, among many others.

The bicycloalkyl and tricycloalkyl radicals may be unsubstituted or substituted in any position, for example, by one or several oxo groups and/or 1 or several alkyl groups that are identical or different such as methyl or isopropyl, and preferably methyl. The junction bond of the bicyclic or tricyclic radical may be located in any position of the molecule. The bond may be located at the level of the bridged carbon atom or one of the other carbon atoms. This bond may also present any position from the point of view of stereochemistry, for example exo or endo. As examples of bicycloalkyl or tricycloalkyl radicals, we can mention camphanyl, bornyl, adamantyl such as 1-adamantyl or 2-adamantyl, caranyl, epiisobornyl, epibornyl, norbornyl or norpinanyl.

Halogen is understood as fluorine, chlorine, bromine or iodine.

The term (C_5-C_{14})-aryl designates:

- either the (C_5-C_{14})-aryl heterocyclic radicals (= (C_5-C_{14})-heteroaryl), in which the carbon atoms of the cycle are replaced by a heteroatom such as nitrogen, oxygen or sulfur,
- or the (C_6-C_{14})-aryl carbocyclic radicals.

Illustrative (C_6-C_{14})-aryl carbocyclic radicals include among others phenyl, naphtyl, biphenylyl, anthryl and fluorenyl, including e.g. 1-naphtyl, 2-naphtyl and phenyl. Phenyl is in some cases preferred.

Unless otherwise indicated, the aryl radicals, in particular phenyl, may be non-substituted or substituted by one or several identical or different radicals chosen from among (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, (C_1-C_8)-alkoxy, halogens such as fluorine, chlorine and bromine, nitro, amino, trifluoromethyl, hydroxyl, methylenedioxy, cyano, hydroxycarbonyl, aminocarbonyl, (C_1-C_4)-alkoxycarbonyl, phenyl, phenoxy, benzyl and benzyloxy. In particular, the aryl radicals such as defined for R^2 may themselves be substituted by the radicals above. In general, at most 2 nitro groups may be used in the compounds of formula (I) according to the invention.

In the case of monosubstituted phenyl, the substituent may be located in position 2, 3 or 4 and preferably in position 3 or 4. In the case where the phenyl is di-substituted, the substituents may be in positions 2, 3 or 2, 4 or 2, 5 or 2, 6 or 3, 4 or 3, 5. Preferably, in the di-substituted phenyls, the two substituents are in positions 3, 4. When the phenyl is tri-substituted, the positions are as follows: 2, 3, 4 or 2, 3, 5 or 2, 3, 6 or 2, 4, 5 or 2, 4, 6 or 3, 4, 5. In the same way, the naphtyl radicals or other aryl radicals may be substituted in any position, for example, the 1-naphtyl radical in position 2-, 3-, 4-, 5-, 6-, 7- and 8 and the 2-naphtyl radical in position 1-, 3-, 4-, 5-, 6-, and 7.

The (C_5-C_{14})-aryl group may also represent a monocyclic or polycyclic aromatic system in which 1, 2, 3, 4 or 5 carbon atoms of the cycle are replaced by heteroatoms, independently selected particularly from nitrogen, oxygen and sulfur. Heterocyclic (C_5-C_{14})-aryl groups (= (C_5-C_{14})-heteroaryl) groups, include among others: 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phtalazinyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, cinnolinyl, _-carbolinyl, and benzo-condensed derivatives, cyclopenta-, cyclohexa-, or cyclohepta- condensed from these radicals. The heterocyclic system may be substituted by the same substituents mentioned above for the carbocyclic system.

Among the heteroaryl radicals, the monocyclic or bicyclic aromatic systems having 1, 2 or 3 heteroatoms are preferred, in particular 1 or 2 heteroatoms chosen from among N, O or S, and which are not substituted or are substituted by groups such as

(C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, fluorine, chlorine, nitro, amino, trifluoromethyl, hydroxyl, (C_1-C_4)-alkoxycarbonyl, phenyl, phenoxy, benzyloxy, and benzyl.

Some preferred compounds comprise 5- to 10-membered monocyclic or bicyclic aromatic ring systems which include 1 to 3 heteroatoms, often 1 or 2 heteroatoms, chosen from among N, O and S and which may be substituted by 1 or 2 substituents such as (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, phenyl, phenoxy, benzyl and benzyloxy.

The optically active carbon atoms contained in the compounds of formula (I) may have the configuration R or the configuration S, independently of each other.

The compounds of formula (I) may be in the form of pure enantiomers or pure diastereoisomers or in the form of a mixture of enantiomers, for example in the form of racemic compounds or diastereoisomer mixtures.

Thus, the object of the present invention is pure enantiomers, mixtures of these enantiomers, pure diastereoisomers and mixtures of these diastereoisomers.

The invention includes mixtures of two or more of the two stereoisomers of formula (I) and all the ratios of these stereoisomers in the said mixtures.

If necessary, the compounds of formula (I) may be present in the form of E isomers or Z isomers. Thus, the object of the invention is pure E isomers, pure Z isomers and E/Z mixtures in any ratio.

The invention also includes different regioisomers connected at the ortho, para or meta position of A^2. Preferably, A^2 is in the para position.

The invention also includes compounds of the formula (I) possibly present in the form of a tautomeric equilibrium. By way of example, when [A^1] represents a phenyl substituted at para with a CO_2H group (A^2 = CO_2H) and in meta with a formyl group (R^2 = CHO), an equilibrium is established between the open and closed form (hydroxylactone).

The diastereoisomers, including the E/Z isomers, may be separated into individual isomers, for example using chiral phase chromatography. The racemic compounds may be separated into two enantiomers by conventional methods such as chromatography or by resolution methods.

The acceptable physiological salts of the compounds of formula (I) are in particular salts that are pharmaceutically useful or nontoxic or physiologically useful.

When the compounds of formula (I) include an acid group such as carboxylic acid, it is a matter of e.g. alkaline metal salts or alkaline earth such as salts of sodium, potassium, magnesium, calcium, and also the salts formed with quaternary ammonium ions that are physiologically acceptable and active salts with acids such as ammonia and physiologically acceptable organic amines such as e.g. triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine. When the compounds of formula (I) contain a base group, they may form an additive salt with the acids, e.g. with the inorganic acids such

as chlorhydric, sulfuric, phosphoric acid or with the organic carboxylic acids such as acetic acid, trifluoroacetic, citric, benzoic, maleic, fumaric, tartaric, methane sulfonic or toluene sulfonic.

The compounds of formula (I) which contain a base group and an acid group may be present in the form of zwitterions (betaine), which are also included in the present invention.

The salts of the compounds of formula (I) may be obtained by the ordinary methods known to the person skilled in the art, for example by combining a compound of formula (I) with an organic or inorganic acid or a base in a solvent or by dispersion or by exchange of cation or anion starting with another salt.

The invention also includes all the salts of compounds of formula (I), which because of their low physiological acceptability, cannot be used directly as medication but can be used as intermediate products to carry out subsequent chemical modifications or as starting products for the preparation of physiologically acceptable salts.

The present invention also includes solvent complexes of the compounds of formula (I), for example hydrates, solvates formed with alcohols, and all the derivatives of compounds of formula (I), for example esters, prodrugs and other physiologically acceptable derivatives as well as the metabolites of the compounds of formula (I).

The invention also includes prodrugs of compounds of formula (I) which may be transformed into compounds of formula (I) in vivo under physiological conditions. The prodrugs of the compounds of formula (I), i.e. the chemically modified derivatives of the compounds of formula (I) in order to obtain improved properties in the desired manner, are known to the person skilled in the art.

For additional information on, and several nonlimiting examples of, suitable types of prodrugs for use in connection with the present invention, see the following: Fleicher et al., Advanced Drug Delivery Review 19 (1996) 115 - 130; Design of prodrugs, H. Bungaard, Ed., Elsevier, 1985; H. Bundgaard, Drugs of the Future 16 (1991) 443; Saulnier et al. Bioorg. Med. Chem. Lett. 4 (1994) 1985; Safadi et al. Pharmaceutical Res. 10 (1993) 1350.

Exemplary prodrugs of the compounds of formula include:

- Prodrugs in the form of esters of carboxylic groups, in particular of the COOH group,
- Prodrugs in the form of esters of phosphate or phosphonate groups,
- Prodrugs in the form of acyl and of carbamate for the groups containing a nitrogen that can be acylated, such as the amino groups. In the acylated prodrugs or those in the form of carbamate, one or more times, for example two times, a hydrogen atom located on the nitrogen atom is replaced by an acyl or carbamate group. From among the preferred acyl or carbamate groups, it is possible to mention the groups $R^{10}CO$-,

$R^{11}OCO$-, in which R^{10} is a hydrogen or a (C_1-C_{18})-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{18})-cycloalkyl-(C_1-C_8)-alkyl, (C_5-C_{14})-aryl radical, in which 1 to 5 atoms of carbon may be replaced by heteroatoms such as N, O, S or (C_5-C_{14})-aryl-(C_1-C_8)-alkyl, in which 1 to 5 carbon atoms in the aryl part may be replaced by heteroatoms such as N, O, S and R^{11} has the same values as R^{10} with the exception of hydrogen.

This invention encompasses an enantiomer or diastereoisomer of the formula (I) characterized in that the carbon in position 3 which holds the -NHCO-[A^1]-A^2 group is present in the S configuration.

The invention also encompasses the diastereoisomers of formula (I) in which the carbon in position 3 which holds the -NHCO-[A^1]-[A^2] is present in the S configuration and the carbon that holds the group -Z such as defined above, with the exception of hydrogen, is present in the S configuration.

Compounds of particular interest include those of formula (I) in which R^1 is a radical R'^1.

Compounds of particular interest also include those compounds of the formula (I) in which R^1 is a phenyl-(C_1-C_8)-alkyl-, phenyl-(C_2-C_8)-alkenyl-, phenyl-(C_2-C_8)-alkynyl-, cyclohexyl-(C_1-C_8)-alkyl, cyclohexyl-(C_2-C_8)-alkenyl-, cyclohexyl-(C_2-C_8)-alkynyl- radical, the said aryls being substituted or non-substituted by one or more R^2 radicals.

Compounds of particular interest further include those compounds of formula (I) in which -[A_1]- represents a group chosen from among -CH(Z)-(C_1-C_4)-alkyl-phenyl-, -phenyl-, -C(Z) = CH-phenyl-, -C(Z) = CH-naphtyl-, -indolyl-, -CH_2-phenyl-, -CH_2-pyridinyl-, the said phenyl, naphtyl, indolyl or pyridinyl radicals being substituted or not substituted by R^2 or R'^2.

Compounds of particular interest further include those compounds of formula (I) in which, when -[A_1]- includes a phenyl group substituted by R^2 or R'^2, R^2 is preferably a -CHO or (C_1-C_4)-alkyloxy-, CO_2H, -CH_2OH, -carbonyl- group and R'^2 is preferably an -OPO_3H_2 or PO_3H_2 group, R^2 and R'^2 especially being in the meta position when A^2 is in the para position.

Compounds of particular interest further include those compounds of the formula (I) in which -A^2 preferably represents -PO (OH) (OH), -OPO (OH) (OH), -CR'fR'gPO (OH) (OH), -O-CR'fR'gPO (OH) (OH); -O-CR'f (CO_2H)2, -CR'fR'g-CO_2H, CR'-(CO_2H)2, -CR'fR'g-CH_2-CO_2H, -CH (CH_2CO_2H) (CH_2CO_2H), -CO_2H or -NHCO- PO (OH) (OH), R'f and R'g, identical or different, representing a halogen atom, especially fluorine or a hydrogen atom.

Compounds of particular interest further include those compounds of formula (I) in which -A^2 represents -O-PO_3H_2, -CF_2-PO_3H_2, -CH_2CO_2H, CHF-CO_2H, –CH(CO_2H)2, –CF(CO_2H)2, or CF_2CO_2H.

Compounds of particular interest also include those compounds of formula (I) in which Z preferably represents NHCORc, $NHCO_2Rc$, in which Rc represents an alkyl radical containing from 1 to 6 carbon atoms.

Compounds of particular interest also include those compounds of formula (I) in which one or several radicals have the specific meanings mentioned above.

Compounds of particular interest also include those compounds of formula (I) (being in any of their possible isomeric forms, alone or in mixture in any ratio whatsoever, as well as their physiologically acceptable salts and/or prodrugs thereof) in which:

R^1 is a radical, phenyl-(C_1-C_8)-alkyl-, phenyl-(C_2-C_8)-alkenyl-, phenyl-(C_2-C_8)-alkynyl-, cyclohexyl-(C_1-C_8)-alkyl-, cyclohexyl-(C_2-C_8)-alkenyl-, cyclohexyl-(C_2-C_8)-alkynyl-, the said aryls being non-substituted or substituted with one or several R^2 radicals;

-[A^1]- is -CH(Z)-(C_1-C_4)-alkyl-phenyl-, -phenyl-, -C(Z) = CH-phenyl-, -C(Z) = CH-naphtyl-, -indolyl-, $-CH_2$-phenyl-, or $-CH_2$-pyridinyl-, wherein the phenyl, naphtyl, indolyl or pyridinyl radicals are not substituted or are substituted with R^2 or R'^2;

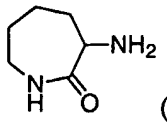
-A^2 is $-O-PO_3H_2$, $-CF_2-PO_3H_2$, $-CH_2CO_2H$, $CHFCO_2H$, $-CH(CO_2H)_2$, $-CF(CO_2H)_2$, or CF_2CO_2H; and/or

Z is NHCORc or $NHCO_2Rc$, in which Rc is an alkyl radical containing 1 to 6 carbon atoms.

Compounds of particular interest also include those compounds of formula (I) prepared in the examples described below as well as their physiologically acceptable salts and their prodrugs.

The present invention also provides synthetic procedures for compounds of formula (I). The compounds may generally be prepared, for example in the course of a convergent synthesis, by coupling of two or more fragments which may be derived by retrosynthesis of the compounds of formula (I). In order to prevent the functional groups from leading to the undesirable or secondary reactions in the course of each synthesis step, it may be advantageous or necessary in the course of synthesis of the compounds of formula (I) to introduce functional groups in the form of precursors, which are then converted into the desired functional group or to temporarily block these functional groups by putting into use an appropriate group protector strategy for the synthesis which is known to the person skilled in the art (Greene, Wuts Protective Group in Organic Synthesis, Wiley 1991).

Thus, the compounds of formula (I) may be prepared, for example, by coupling an amine of the formula (II)

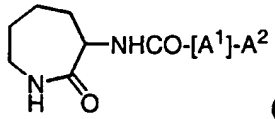

(II)

where, if necessary, the functional group is in the form of the precursor or in protected form, with

a) either at first with an acid or an acid derivative of the formula (III)

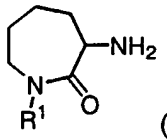
$$X\text{-}C(=O)\text{-}[A^1] - A'^2 \qquad \text{(III)}$$

in which $[A^1]$ is as defined above in the formula (I) and A'^2 representing, in addition to the values of A^2, the hydroxy radical, X is a group that can be substituted by a nucleophile or where, if necessary, the functional groups are in the form of precursors or in protected form, in order to obtain a compound of the formula (I')


(I')

then R^1-X' is allowed to react, R^1 being as defined above and X' preferably being an iodine, a promine or a mesylate group; the said functional groups possibly present in the form of precursor or in the protected form being then converted into groups present in the compounds of formula (I);

b) or at first with R^1-X', in order to obtain, after deprotection if necessary, the compound of the formula (I'')


(I'')

then with acid or the acid derivative of formula (III), the said functional groups possibly present in the form of the precursor or in the protected form, being then converted into groups present in the compounds of formula (I).

If desired or if necessary, certain compounds of formula (I) may be subjected to one or more of the following reactions in an appropriate order:

- Action of a monodebenzylation agent when $[A'^2]$ represents OPO $(OBn)_2$,
- Action of a total deprotection agent,

- Action of H-P (O) (ORd) (ORe) when A'^2 represents OH,
- Obtaining different values of Z (NHCORc, NHSORc, $NHCO_2Rc$, $NHSO_2Rc$) starting with the corresponding amine ($Z = NH_2$),
- Saponification, then decarboxylation of the malonic derivative,
- Reduction of the double bond when -[A^1]- represents a -C (Z) = CH-(C_0-C_2)-alkyl-(C_5-C_{14})-aryl group,
- Separation of the enantiomers or the diastereoisomers,
- Salification.

When [A'^2] = OH, the phosphorylation reaction is carried out with HP (O) (ORd) (ORe) in the presence of N'N-disopropylethylamine (DIPEA) and of N,N-dimethylaminopyridine (DMAP) in acetonitrile in the presence of carbon tetrachloride.

The COX group in the formula (III) is preferably the carboxylic acid group or an activated derivative of carboxylic acid. X is e.g. hydroxyl or halogen, in particular chlorine or bromine, alkoxy, preferably methoxy or ethoxy, aryloxy, for example phenoxy, pentafluorophenyloxy, phenylthio, methylthio, 2-pyridylthio or an azotized heterocycle connected by way of a hydrogen atom, in particular a nitrogen such as e.g. 1-imidazolyl. X may also be e.g. (C_1-C_4)-alkyl-O-CO-O- or tolylsulfonyloxy and the activated acid derivative may be a mixed anhydride.

If X is a hydroxyl, thus if the amine of formula (II) reacts with a carboxylic acid of formula (III), then the carboxylic acid is activated at first. The activation may be carried out, for example, with dicyclohexylcarbodiimide (DCCI) or with O-((cyano(ethoxycarbonyl)-metylene)amino)-1,1,3,3-tetramethyluronium tetrafluoroborate (TOTU; König et al., Proc. 21st Europ. Peptide Symp. 1990 (Eds Giralt, Andreau), Escom, Leiden 1991, p. 243) or other activating agents currently used in peptide synthesis.

Other than the free amines of formula (II), the amine salts may also be used in the reaction with compounds of formula (III), the free amines being formed in situ or by a separate step using a base.

The reaction of an activated derivative of carboxylic acid of the formula (III) with the amine (or derivative) of formula (II) is preferably carried out in a manner known in and of itself in a protic or aprotic, but inert, organic solvent. In this case, solvents are used such as methanol, isopropanol, tert-butanol, dimethylformamide or tetrahydrofurane at temperatures going from 0° C to the reflux temperature of these solvents, in particular during the reaction of methyl or ethyl esters (X is a methoxy or an ethoxy) with the amines.

The reactions of the acids of formula (III) (COX = CO_2H) with the free amines are advantageously carried out in an inert aprotic solvent such as dimethylformamide, tetrahydrofurane, dimethoxyethane, or dioxane, if necessary adding a base such as e.g.

potassium tert-butoxide, sodium methoxide or an organic base such as N-methylmorpholine. However, water may also be used as a solvent in the reactions of compounds of formula (II) with amines of the formula (III), for example by using a base such as sodium hydroxide.

If X is chlorine, the reaction will preferably be started with the addition of an acid trap, for example a base or an excess of amine (or derivative). The reaction mixture is then treated and, if desired, the reaction product is purified according to the methods known to the person skilled in the art. The acylation reaction using the compound of the formula (III) $[A^2]$-$[A^1]$-COOH is carried out in particular in the presence of EDC (chlorhydrate 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide) and HOBt (1-hydroxybenzotriazole) in an aprotic dipolar solvent such as dimethylformamide. This reaction may be carried out in solution as a solid phase as the examples below show.

The alkylation reaction using R^1-X' is carried out according to the usual methods known to the person skilled in the art, in particular when X' is a chlorine or a bromine in the presence of a base such as sodium hydride in an aprotic dipolar solvent such as dimethylformamide.

The protecting groups that may be present in the compounds obtained using the compounds of formula (II) and (III) are then eliminated by the classic procedures; for example, the tertbutyl ester groups are converted into carboxylic acid by treatment with the trifluoroacetic acid, the benzyl groups are eliminated by hydrogenation or even the fluorenylmethoxycarbonyl groups are eliminated in the presence of secondary amine and other reactions are carried out using the standard procedures, for example by acylation reactions. If necessary, the conversion into physiologically acceptable salts is carried out by the procedures known to the person skilled in the art.

When the amine is protected ($NHCO_2Rb$), in particular it is protected by a Boc group. The return to free amine may be carried out by the action of trifluoroacetic acid.

When this amine is protected by CO_2CH_2Ph, the deprotection is carried out preferably in the presence of $Pd(OH)_2$, MgO in cyclohexadiene in reflux.

In order to obtain a monodebenzylation ($[A^2]$ = OP (O) (OH) OBn)), in particular sodium iodide is used and the reaction is carried out under reflux of acetone or DABCO (1,4-diazabicyclo[2, 2, 2]octane) in toluene.

In order to obtain total deprotection ($[A^2]$ = OP (O) $(OH)_2$), preferably a classic hydrogenation is carried out in the presence of Pd/C at 10% or trifluoroacetic acid will be used in dichloromethane.

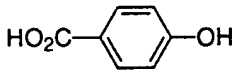
When Z = NH_2, the functionalization reactions in order to obtain different values of Z, objects of the invention, are carried out according to the classic methods of organic synthesis known to the person skilled in the art and are illustrated in the examples described below. The reactions of saponification, decarboxylation, reduction

of the double bond and separation of the enantiomers and diastereoisomers and salification are carried out according to the methods known to the person skilled in the art.

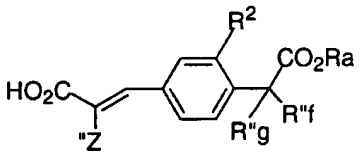
The invention thus provides a procedure such as described above in which the compound of formula (III) is chosen from among the following phosphorylated tyrosines:

N-Boc-Tyr-O-(PO_3Bn_2), N-Ac-Tyr-O-(PO_3Bn_2),
N-Boc-Tyr-CF_2-(PO_3Et_2), N-Ac-Tyr-CF_2- (PO_3Et_2)

or the following benzoic derivatives (IIIa) or benzenic derivatives (IIIb)



(IIIa)



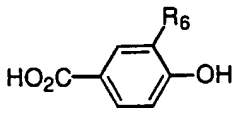
(IIIb)

in which R"f represents an atom of hydrogen, fluorine or CO_2Rd, R"g represents an atom of hydrogen or fluorine and Z" represents NHCORb or $NHCO_2Rb$, the compound of formula (IIIb) presenting an E or Z configuration. Thus, the object of the invention is the procedures described above and the new intermediate compounds of the formulas (IIIb), (I') and (II").

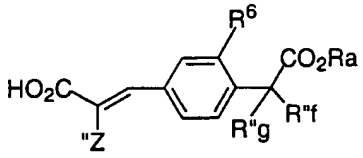
The initial compounds of formula (II), which are then connected with the compounds of formula (III) and R^1-X' to give the compounds of formula (I), are known (the L-alpha-amino-epsilon-caprolactam is commercial; Aldrich).
The compounds of formula (III) are known, may be prepared according to the procedures described in the literature or are even accessible by analogy. By way of example, the O-[bis(phenylmethoxy)phosphinyl]-N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosine (N-Boc-Tyr-O-(PO_3Bn_2)) is a commercially available product (Peninsula).

The preparation of the compounds of formula (III) in which -[A^1]- represents a -C(Z) = CH-(C_0-C_2)-alkyl-(C_5-C_{14})-aryl group (compounds of formula (IIIb)) is illustrated in the diagram below, it being understood that the present invention is not restricted to these syntheses or these initial products. The person skilled in the art will readily appreciate various modifications to the syntheses described herein for the preparation of other compounds of formula (III) according to the invention.

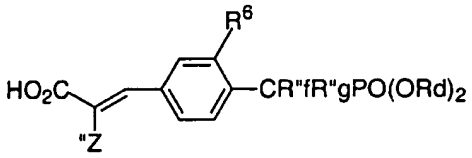
The invention further provides a procedure such as described above in which the compound of formula (III) is chosen from among the phosphated tyrosines: N-Boc-Tyr-O-(PO_3Bn_2), N-Ac-Tyr-O-(PO_3Bn_2), N-Boc-Tyr-CF_2-(PO_3Et_2), N-Ac-Tyr-CF_2-(PO_3Et_2) or the following benzoic derivatives (IIIa, IIIc)) or benzenic derivatives (IIIb, IIId)):



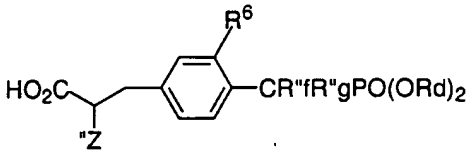
(IIIa)



(IIIb)



(IIIc)



(IIId)

in which R"f represents an atom of hydrogen, of fluorine or CO_2Rd, R"g represents an atom of hydrogen or fluorine and Z" represents NHCORb or $NHCO_2Rb$, R_6 is such as defined.

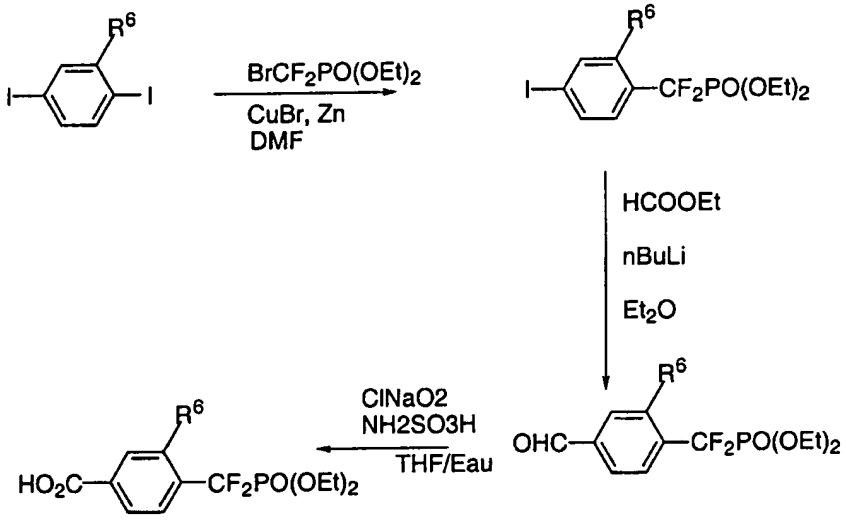
The initial compounds of the formula (III) are commercially available, may be prepared according to the procedures described in the literature and are also synthetically accessible by analogy. By way of example, use of the following products of formula (III) if of particular interest:

- O-[bis(phenylmethoxy)phosphinyl]-N-[(1,1-dimethylethoxy)carbonyl]-L-tyrosine:
(N-Boc-Tyr-O-(PO_3Bn_2), origin: Peninsula Laboratories, Inc.
- N-acetyl-O-[bis-(diphenylmethoxy)phosphinyl]-L-tyrosine: N-Ac-Tyr-O-(PO_3Bn_2)
- N-[(1,1-dimethylethoxy)carbonyl]-4-[bis-ethoxyphosphinyl)difluoromethyl]-L-phenylalanine: N-Boc-Tyr-$CF_2(PO_3Et_2)$
- N-acetyl-4-[bis-ethoxyphosphinyl)difluoromethyl]-L-phenylalanine: N-Ac-Tyr-CF_2-(PO_3Et_2)

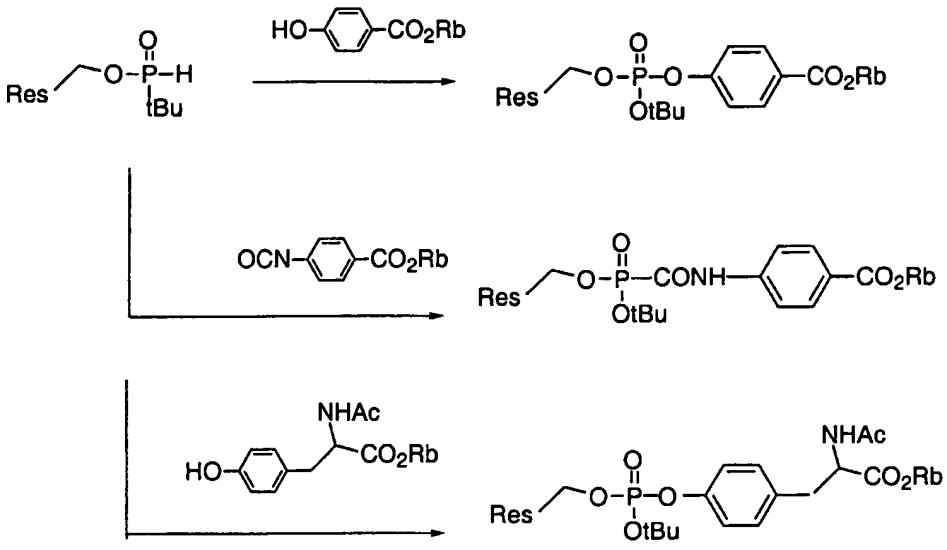
On the preparation of compounds of formula (III) in which -[A_1]- represents a -C(Z) = CH-(C_5-C_{14})- group:

If N-fluorobenzene sulfoniimide (NFSI) or the potassium hexamethyldisilizane (KHMDS) / N-fluorobenzene sulfoniimide (NFSI) mixture is allowed to react prior to the Heck reaction, R"f and R"g represent a fluorine atom in the compounds of formula (IIIb). If the goal is to obtain only esters of formula (B), the decarboxylation reaction may be carried out in the presence of APTS, TFA or PPTS. Compounds of the formula (IIIb) having an E or Z configuration are obtained or an E/Z mixture depending on the nature of the substituents. The formation of malonic acids using the corresponding terbutyl ester may be carried out with formic acid. Catalytic hydrogenation makes it possible to obtain the corresponding reduced compounds. It is also possible to envision the formation of corresponding reduced compounds by zinc coupling of an iodoserine with iodized malonic ester of the formula (A) according to the methods known to the person skilled in the art.

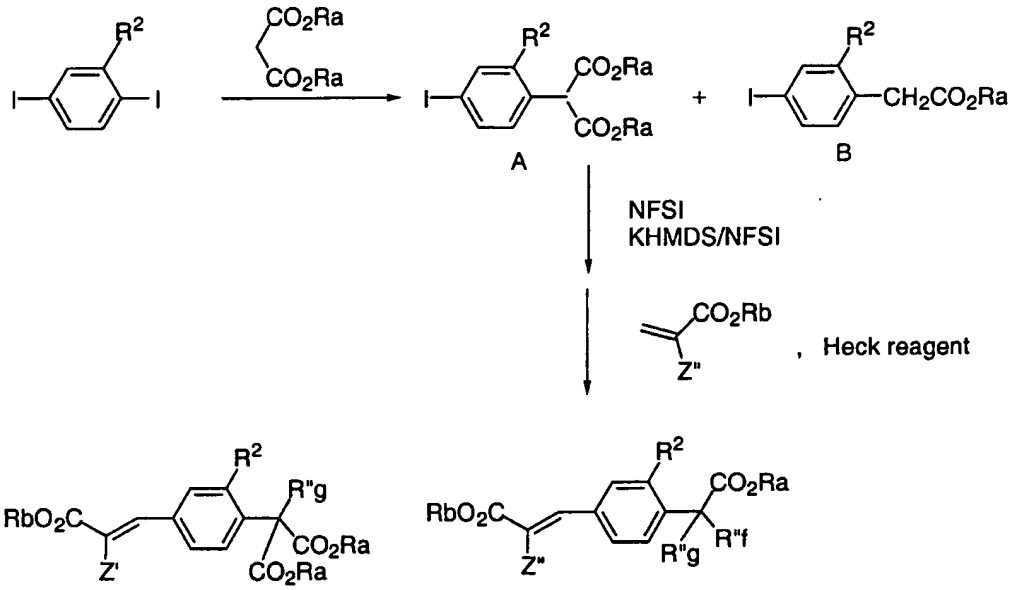
The preparation of compounds of formula (III) in which -[A1]- represents a phenyl group and A2 represents a -$CF_2PO(OEt)_2$ group (compounds of formula (IIIc)) is illustrated in the diagram below (diagram 3):



The compounds of formula (III) may also be prepared in solid phase. The solid phase is prepared according to a publication by Mjalli et al. (Tetrahedron letter, 1996, 6073). The resin is placed in reaction with either a phenol in the presence of CCl_4 and of DMAP, or with a base such as DBU and an isocyanate to generate phosphate and amidophosphonate, respectively. Once the coupling with the compounds of formula (II) has been carried out, still in solid phase, cutting with TFA makes it possible to regenerate the product (diagram 4).



The compounds of formula R5-X' are known, may be prepared according to the procedures described in the literature and are also synthetically accessible by analogy. Halogen derivatives are of particular interest.



When the N-fluorobenzene sulfoniimide (NFSI) or the potassium hexamethyldisilizane (KHMDS) / N-fluorobenzene sulfoniimide (NFSI) is reacted prior to the Heck reaction, R"f and R"g represent a fluorine atom in the compounds of

formula (IIIb). If the goal is to obtain only esters of formula (A), the decarboxylation reaction may be carried out in the presence of APTS or PPTS. Compounds of the formula (IIIb) are obtained having an E or Z configuration or an E/Z mixture depending on the nature of the substituents.

The compounds of formula R^1-X' are known, may be prepared according to the procedures described in literature and are also synthetically accessible by analogy. Halogen derivatives are of particular interest.

Compounds of formula (I) may be used to inhibit the biological activity of Src, Src family members or other SH2-containing proteins.

Of particular interest is the use of compounds of formula (I) to inhibit the complexation or interaction of a Src protein with a phosphorylated protein ligand.

Various mechanisms for inhibition of Src function include inhibition of ligand binding to the Src SH_2 or SH3 domain and inhibition of Src's catalytic domain (tyrosine kinase). Without intending or wishing to be bound by any one theory, the compounds of this invention are thought to exert their biological activity by virtue of their affinity to SH2 domains, and in particular, to the SH2 domain of Src.

The compounds of formula (I) may thus be used to inhibit functioning of one or more SH2-containing proteins, especially Src, in a method comprising administering to the patient whose treatment requires inhibition of the SH2-containing protein, an inhibiting quantity of the compound according to the invention.

The action of the compounds of formula (I) may be demonstrated, for example, in a test in which the inhibition of the bond of the radiolabeled ligand EPQpYEEIPIYL to the protein SH2 is determined by Scintillation Proximity Assay (SPA). Information on this test is given below. As antagonists of the Src SH2 domain, the compounds of formula (I) and their physiologically acceptable salts and their prodrugs are generally good for the treatment or prevention of illnesses connected with interactions between the SH2 domain and their ligands or which may be influenced by the inhibition of interactions of this type, to relieve or heal when an inhibition of the interactions of this type is desired. As was explained at the beginning, an interaction such as this plays a significant role in bone resorption.

The compounds of formula (I) are most particularly antagonists of the human Src SH2 receptor and are thus capable, for example, of inhibiting the adhesion of the osteoclasts on the surface of the bone and thus bone resorption by the osteoclasts.

Bone diseases of which the treatment or prevention requires the use of compounds of formula (I) or their prodrugs include in particular osteoporosis, hypercalcemia, osteopenia, for example caused by bone metastases, dental disorders, e.g. parodontitis, hyperparathyroidism, periarticular erosion in rheumatoid arthritis, Paget's disease, osteopenia induced by immobilization. In addition, compounds of formula (I) may be used to relieve, prevent or treat bone disorders that are caused by

treatments, by glucocorticoids, therapies connected with the use of steroids or corticosteroids or because of male or female sexual hormone deficiencies.

All of these disorders are characterized by a loss of bone which is based on a lack of equilibrium between bone formation and bone destruction and which may be influenced favorably by inhibition of bone resorption by the osteoclasts.

The compounds according to the invention, by their affinity with the Src-SH2 domain, may also be used in other therapeutic applications. For example, it is known that the platelets and the neurons are the tissues which also express Src-SH2. In addition, several proteins in this family are largely expressed in the hematopoietic system; numerous applications in the treatment of immunity, infection, allergy and autoimmune diseases can be foreseen.

Finally, the compounds of formula (I) may also be used to inhibit the bond of a protein containing the SH2 domain, other than Src, to an analog phosphorylated protein, the method consisting of administration to the patient whose treatment requires inhibition of the SH2 domain of an inhibiting quantity of the compound according to the invention. The proteins containing the SH2 domain other than Src are chosen from among Fyn, Lck, Yes, Blk, Lyn, Fgr, Hck, Yrk, Abl and Zap 70.

The compounds of this invention may thus be used in the treatment of diseases such as proliferative diseases, cancer, restenosis, inflammation, allergies or cardiovascular diseases.

From among these products, the invention most particularly has as its object, as a medications, the compounds of formula (I) listed above.

Thus, the object of the present invention is a compound of formula (I), and/or its physiologically acceptable salts and/or its prodrugs, as a medication.

The present invention most particularly has as its object a compound of formula (I), and/or its physiologically acceptable salts and/or its prodrugs, as a medication having an antagonist activity to the Src SH2 receptor.

The present invention most particularly has as its object a compound of formula (I), and/or its physiologically acceptable salts and/or its prodrugs, as a medication having an activity that inhibits bone resorption or for the treatment or prevention of osteoporosis.

The present invention most particularly has as its object a compound of formula (I), and/or its physiologically acceptable salts and/or its prodrugs, as a medication for the treatment or prevention of immunity, infection, allergy and autoimmune diseases.

The present invention most particularly has as its object a compound of formula (I), and/or its physiologically acceptable salts and/or its prodrugs, as a medication for the treatment or prevention of diseases such as proliferative diseases, cancer, restenosis, inflammation, allergies or cardiovascular disease.

The present invention most particularly has as its object a compound of formula (I) and/or its physiologically acceptable salts and/or their prodrugs for the preparation of medications intended for the prevention or treatment of osteoporosis.

The present invention most particularly has as its object a compound of formula (I) and/or its physiologically acceptable salts and/or their prodrugs for the preparation of medications intended for the treatment or prevention of immunity, infection, allergy and autoimmune diseases.

The present invention most particularly has as its object a compound of formula (I) and/or its physiologically acceptable salts and/or their prodrugs for the preparation of medications intended for the treatment or prevention of diseases such as proliferative diseases, cancer, restenosis, inflammation, allergies or cardiovascular disease.

The compounds of formula (I) as well as their physiologically acceptable salts and their prodrugs may be administered to animals, preferably to mammals and in particular to human beings as medications for therapy or prophylaxis.

They may be administered as they are or in a mixture with one or several other compounds of formula (I) or even in the form of a pharmaceutical preparation (pharmaceutical compound) which makes possible an enteral or parenteral administration and which includes an effective dose of at least one compound of formula (I) and/or its physiologically acceptable salts and/or its prodrugs as well as the current agents and/or additives that are pharmaceutically inert.

The medications may be administered orally, for example in the form of pills, tablets, coated tablets, coatings, granules, capsules and soft capsules, solutions, syrups, emulsions, suspension or aerosol mixture.

However, the administration may also be carried out rectally, for example in the form of suppository or parenterally, for example in the form of injectable solutions or infusion solutions, of microcapsules or implants or percutaneously, for example in the form of pomade, solution, pigments or colorants, by transdermic means (patches) or by other means such as an aerosol form or nasal spray.

The pharmaceutical compounds according to the invention are prepared according to the methods known in and of themselves, of organic or inorganic pharmaceutically inert agents being added to the compounds of formula (I) and/or their physiologically acceptable salts and/or their prodrugs.

For the production of pills, tablets or coated tablets and gelatin capsules, it is possible to use, for example, lactose, cornstarch or its derivatives, talc, stearic acid or its salts, etc. The agents appropriate for soft gelatin capsules or for suppositories include, for example, fats, waxes, semi-solid or liquid polyols, natural or modified oils, etc.

The vehicles appropriate for preparation of solutions, for example injectable solutions, emulsions or syrups include e.g. water, alcohols, glycerol, the polyols, sucrose, inverted sugars, glucose, vegetable oil, etc. The agents that are appropriate for microcapsules or implants include e.g. glyoxilic acid copolymers and lactic acid. The pharmaceutical preparations normally contain 0.5% to 90% by weight of compounds of formula (I) and/or their physiologically acceptable salts.

In many of the active ingredients and the agents, the pharmaceutical preparations may contain additives such as e.g. diluants, disintegrators, bonding agents, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweetening agents, colorings, flavoring compounds or aroma compounds, thickeners, buffers and also solvents or solubilizers or agents to obtain a delayed effect and also salts to modify the osmotic pressure, coating agents or antioxidants.

They may also contain two or more compounds of formula (I) and/or their physiologically acceptable salts and/or their prodrugs. Besides that, in addition to at least one or several compounds of formula (I) and/or their acceptable physiological salts and/or their prodrugs, they may contain at least one or more other active ingredients that can be used in a therapeutic or prophylactic manner.

Thus, the object of the present invention is pharmaceutical compounds which make possible enteral or parenteral administration and which contains, by way of the active compound, an effective dose of at least one compound of formula (I) and/or its physiologically acceptable salts and/or its prodrugs and one or more inert pharmaceutical agents and/or one or more of the usual additives.

When the compounds of formula (I) are used, the doses may vary within large limits and must be set as a function of the person to be treated. This depends, for example, on the compound used and the nature and the severity of the illness to be treated and whether there is an acute or chronic condition or whether a prophylactic treatment is being used.

The pharmaceutical preparations (pharmaceutical compounds) normally contain from 0.2 to 500 mg, and preferably 1 to 200 mg, of the compound of formula (I) and/or its physiologically acceptable salts and/or its prodrugs.

In case of oral administration, the daily dose generally varies from 0.01 to 100 mg/kg and preferably from 0.1 to 50 mg/kg, in particular 0.1 to 5 mg/kg. For example, for a 75 kg adult, it is possible to envision a daily dose that varies from 0.3 to 0.5 mg/kg.

In the case of intravenous administration, the daily dose varies approximately from 0.01 to 100 mg/kg and preferably from 0.05 to 10 mg/kg.

The daily dose may be divided, in particular in the case of administration of a large quantity of active ingredient, into several, e.g. 2, 3 or 4 parts. If necessary, as a function of individual behavior, it may be necessary to administer different doses in an

increasing or decreasing manner. In addition to the use of compounds of formula (I) as medications, it is also possible to envision their use as a vehicle or support of the active components in order to transport these active components in a specific manner to an action site (Drug targeting, see Targeted Drug Delivery, R.C. Juliano, Handbook of Experimental Pharmacology, Vol. 100, Ed. Born, G.V.R. et al, Springer Verlag). The active compounds which may be transported are in particular those used for treatment or prevention of the diseases mentioned above.

The compounds of formula (I) and their salts may also be used as a diagnostic agent, for example for in vitro methods or as an auxiliary in biochemical studies in which the goal is to antagonize the human SRC SH2 domain. In addition, they may be used as intermediates for the preparation of other compounds, in particular active ingredients which are accessible starting with the compounds of formula (I), for example by modification or introduction of radicals or functional groups.

Examples

The following examples illustrate the invention without limiting it in any way. The products have been identified by mass spectroscopy (MS), infrared (IR) and/or by nuclear magnetic resonance (NMR).

Abbreviations/chemical names:

AcOEt: ethyl acetate; EDC: 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide chlorhydrate; DCC: 1,3-dicyclohexylcarbodiimide; DMF: dimethylformamide; DMSO: dimethylsulfoxide; DBU: 1,8-diazabicyclo[5,4,0]undec-7-ene; DPPA: diphenylphosphorylazide; DMSO: dimethylsulfoxide; HOBt: 1-hydroxybenzotriazol hydrate; MeOH: methanol; TEA: triethylamine; TFA: trifluoroacetic acid; THF: tetrahydrofuran; MCPBA: meta-chloroperbenzoic acid; Pd/C: Palladium on coal; Boc: terbutoxycarbonyl; CBz: benzyloxycarbonyl; TMSBr: bromotrimethylsilane; TMSI: trimethylsilane iodide; IR: infrared; NMR: Nuclear Magnetic Resonance; MS: Mass Spectroscopy; ep.: shoulder; S: strong; s: singlet; d: doublet; t: triplet; quad: quadruplet; quint: quintuplet; l: large; m: multiplet or massive; J: bonding constant; Rf: chromatographic retention time.

Preparation P1: **(3S)-3-amino-1-[[(1,1'-biphenyl)-4-yl]methyl]-hexahydro-2H-azepin-2-one**

Step a: Protection

N-[(3S)-hexahydro-2-oxo-1H-azepin-3-yl]-carbamate 1,1-dimethylethyl

To a solution of 5.12 g of (3S)-3-amino-hexahydro-2H-azepin-2-one (Aldrich) in 75 ml of dichloromethane, 8.73 g di-terbutyl dicarbonate is added in fractions while cooling using an ice water bath and the mixture is agitated one hour at ambient temperature. Washing is carried out with water, drying

and evaporation under reduced pressure to obtain 8.9 g of the product expected. S = 148°C

NMR (1H, DMSO)

1.44 (s, 9H); 1.20 at 2.15 (m, 6H); 3.20 (m, 2H); 4.31 (m, 1H); 5.92 (d, 1H); 6.00 (sl, 1H).

Step b: Alkylation

N-[(3S)-1-[[(1,1'-biphenyl)-4-yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-carbamate 1,1-dimethylethyl

To 23 ml of THF, 1.17 g of 1,1'-biphenyl, 4-(bromomethyl), 1.08 g protected amine (N-Boc) prepared in the preceding step, 0.265 g potassium hydroxide and 0.35 g of transfer catalyst of the tetrabutyl-ammonium iodide phase is added, agitated at ambient temperature overnight, the THF is evaporated, absorbed with dichloromethane, washed with water, dried and evaporated under reduced pressure until 2.1 g of gross product is obtained, which is purified by chromatography by eluting with dichloromethane, then the mixture CH_2Cl_2/AcOEt 95/5 to obtain 1.4 g of the purified product.

Step c: Deprotection

(3S)-3-amino-1-[[(1,1'-biphenyl)-4-yl]methyl]-hexahydro-2H-azepin-2-one

A solution of 1.4 g of the product obtained in the preceding step is agitated for 2 hours in a CH_2Cl_2/TFA 50/50 mixture, then evaporated under reduced pressure and the residue obtained is absorbed with dichloromethane, washed with an aqueous solution of sodium bicarbonate, then with salt water. The organic solution is dried on $MgSO_4$ and evaporated to lead to the expected compound.

NMR (1H, $CDCl_3$)

1.25 (m, 1H) and 1.70 (m, 1H); 1.60 (m, 2H); 1.92 (m, 2H); 3.24 (dd, J = 5 and 15 Hz, 1H); 3.44 (dd, J = 11, 5 and 15 Hz, 1H); 3.79 (dl, J = 9 Hz, 1H); 4.51 (d, J = 14.5 Hz, 1H); 4.82 (d, J = 14.5 Hz, 1H); 7.33 (d, 2H); 7.54 (d, 2H); 7.55 (m, 2H); 7.43 (m, 2H); 7.34 (m, 1H)

MS

$295^+ = [M + H]^+$; $336^+ = MNa^+ + CH_3CN$; $594^+ = [2M + H]^+$; $167^+ = Ph\text{-}Ph\text{-}CH_2^+$

<u>Preparation of a resin containing the compound of formula (III)</u>: **N-acetyl-O-[[(1,1-dimethyl)ethoxy]methoxyphosphinyl]-D-tyrosine supported on a Wang resin (P2).**

Step a) N-acetyl-O-[[(1,1-dimethyl)ethoxy]methoxyphosphinyl]-D-tyrosinate 2-propenyl supported on a Wang resin (Res-CH_2-OPO (OtBu)-O-Ph-CH_2-CH(NHAc)-CO_2-CH_2-CH = CH_2)

- 2 g of the salt of triethylammonium methoxyphosphinyl is mixed on a Wang resin (Res-CH_2-O-PO (H) (O^+, N^+Et_3) described by A.M. Mjalli, Tet Lett, 1996, 37(34)

6073) with 20 ml of a solution of 5 ml of tert-butanol and 45 ml acetonitrile, agitated 10 minutes by nitrogen bubbling and filtered.

- This resin is then mixed with 10 ml of a solution of 5 ml of tert-butanol and 45 ml of acetonitrile, then 10 ml of a solution of 2.4 ml of tBuCOCl, 10 ml of acetonitrile and 10 ml of pyridine, agitated 15 minutes, filtered and washed with acetonitrile.
- The resin is absorbed with 20 ml acetonitrile and a solution of 1.4 ml of CCl_4, 2.5 ml of diisopropylamine, 2.5 ml of D-tyrosinate of 2-propenyl (OH-Ph-CH_2-CH(NHAc)-CO_2-CH_2-CH = CH_2), 200 mg of DMAP and 15 ml of acetonitrile are added, agitated 45 minutes, washed with acetonitrile, then with dichloromethane.

Step b) Deprotection of the acid function

N-acetyl-O-[[1,1-dimethyl)ethoxy]methoxyphosphinyl]-D-tyrosine supported on a Wang resin

1 g of the previously prepared resin, 12.5 ml of a solution of 27 ml DMF, 3 ml acetic acid and 0.3 ml N-methylmorpholine are placed in a frit column and agitated 15 minutes with argon bubbling. Then 100 mg of Pd(PPh3)4 is added under argon bubbling, agitated 1 hour and 30 minutes under argon bubbling, 40 mg of $Pd(PPh_3)_4$ is added again and agitated 30 minutes with argon bubbling. After filtering and washing (DMF, DMF/$CHCl_3$ then DMF), the resin containing the phosphated tyrosine of formula (III) is obtained.

EXAMPLE 1:

N2-acetyl-N-[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide

R^1: CH_2-Ph-Ph; -[A^1]-: CH(NHAc)-CH_2-phenyl-; A^2: -OPO_3H_2

(3S, 2S) (asymmetrical carbon in position 3 of the caprolactam and asymmetrical carbon in position 2 of the phenylalaninamide).

Step a: Coupling

N-[(2S)-1-[[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino]-1-oxo-3-4[[bis(phenylmethoxy)phosphinyl]oxy]-phenyl]-2-propyl]-carbamate 1,1-dimethylethyl

A solution of 406 mg of N-Boc-Tyr-O-(PO_3Bn_2) (2S) (from Peninsula), 143 mg EDC, HCl and 101 mg of HOBt are agitated for 15 minutes at ambient temperature in 8 ml of dichloromethane and 0.8 ml of dimethylformamide and then drop by drop a solution is added of 220 mg of the product prepared in step C of preparation 1, in 4 ml of dichloromethane. The mixture is agitated 2 hours 30 minutes at ambient temperature, then dichloromethane is added, then the organic phase is washed with a solution of 5 ml of sodium bicarbonate, then with salinated water, dried on magnesium sulfate and evaporated. The gross product is purified by chromatography on silica

eluted with the mixture CH_2Cl_2/MeOH 96/4 to obtain 500 mg of the product expected, which is recrystallized in ether. S = 140°C

NMR (1H $CDCl_3$)

1.41 (s, 9H); 1.21 (m, 2H); 1.73 (m, 2H); 1.86 (m, 1H); 1.43 (m, 1H); 2.04 (m, 1H); 4.58 (dd, 1H); 7.45 (masked, 1H); 3.07 (d, 2H); 4.41 (q, 1H); 4.94 (dl, 1H); 3.25 (dd, 1H); 3.47 (dd, 1H); 4.48 (d, 1H); 4.77 (d, 1H); 5.10 (d, 4H); 7.10 ([AA'BB'], 4H); 7.31 (m)-7.43 (m) 15H; 7.57 (m, 4H).

Step b: Deprotection of the amine

N-[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-[[bis(phenylmethoxy)phosphinyl]oxy]-L-phenylalaninamide

162 mg of paratoluene sulfonic acid (APTS, H_2O) is added to a suspension of 350 mg of the protected amine prepared in the preceding step in 6 ml acetonitrile in nitrogen atmosphere and agitated overnight at ambient temperature. Absorption with dichloromethane is carried out, washing with a solution of sodium bicarbonate, then salinated water, drying and evaporating to obtain the gross product that is purified by chromatography, eluted
with the mixture CH_2Cl_2/MeOH 90/10. 300 mg free amine expected is obtained.

MS

$718^+ = MH^+$; $740^+ = MNa^+$; $295^+ = MH^+$ - Tyr(OBn) 396^+; $167^+ = CH_2$-Ph-Ph; $91^+ = PhCH_2^+$

Step c: Acylation of the amine

N2-acetyl-N-[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-[[bis(phenylmethoxy)phosphinyl]oxy]-L-phenylalaninamide

Drop by drop, 0.048 ml of acetic anhydride is added to a solution of 300 mg amine prepared in the preceding step in 3 ml pyridine, cooled using an ice bath, allowed to recover at ambient temperature and agitated for 2 hours 30 minutes. After evaporation, the gross product is purified by chromatography eluted with the CH_2Cl_2/MeOH 95/5 mixture.

250 mg of the expected acylated amine is obtained.

MS

(ES Electro Spray: positive mode)

$760^+ = MH^+$; $782^+ = MNa^+$; $295^+ = MH^+$ - $COCH(NHAc)CH_2Ph$-$OPO(OBn)_2$; $167^+ = -CH_2$-Ph-Ph; $91^+ = PhCH_2^+$

(ES Electro Spray: negative mode)

$758^- = [M-H]^-$

$668^- = 758^-$ - (CH_2Ph)

Step d: Total deprotection

N2-acetyl-N-[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide

250 mg of dibenzylphosphate ester is dissolved in 8 ml methanol and hydrogenated 3 hours 30 minutes in hydrogen atmosphere in the presence of Pd/C (catalytic quantity). After filtering on cellite, it is washed with CH_2Cl_2/MeOH, evaporated and the gross product is recrystallized in acetonitrile. 120 mg of the product expected is obtained.

NMR (1H, DMSO)

1.10 to 1.90 (m, 6H); 1.78 (s, 3H); 2.72 (m, 2H); 3.07 (dd, 1H); 3.30 (dd, 1H); 3.58 (dd, 1H); 4.52 (m, 3H); 4.62 (m, 1H); 7.06 (d, 2H) 7.24 (d, 2H) [AA'BB']; 7.36 (m, 3H); 7.46 (t) 2H; 7.65 (m, 4H); 8.07 (d, 1H); 8.19 (d, 1H).

(ES Electro Spray: positive mode)

$580^+ = MH^+$

(ES Electro Spray : negative mode)

$578^- = [M-H]^-$

IR (Nujol)

OH/NH absorption region; C = O 1633 cm-1; aromatic amide II 1543, 1507 and 1487 cm-1.

The same compound has also been obtained starting with the resin obtained in step b of preparation 2 (P2). 50 g of the amine obtained in step 3 of preparation 1 in 2 ml dichloromethane, 110 mg of the HOBt in 1 ml of DMF, 0.12 ml of diisopropylcarbodiimide in 1 ml of DMF are added to 200 mg of the resin (P2). The solution is left to stand overnight at ambient temperature, then washed with DMF, DMF/CH_2Cl_2, then CH_2Cl_2. To the resin obtained, 3 ml of TFA at 15% in CH_2Cl_2 is added, agitated 2 hours, filtered and evaporated to obtain the compound expected.

EXAMPLE 2:

[(2S)-1-[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino]-1-oxo-3-[4-(phosphonooxy)phenyl]propyl] carbamate 1,1-dimethylethyl

R^2: -CH_2-Ph-Ph; -[A^1]-: -CH(NHBoc)-CH_2-phenyl-;

A^2: -OPO_3H_2 (3S, 2S)

The procedure is as in example 1, step D, but immediately starting with the N-Boc derivative prepared in step A of example 1.

NMR (1H, DMSO)

1.25-1.68-1.44-1.84 (m, 6H); 1.32 (s, 9H); 2.72 (m, 1H); 3.04 (dl, 1H); 4.12 (tl, 1H); 7.16 (dl, 1H); 3.27 (m, 1H); 3.61 (dd, 1h); 4.47 (d, 1h); 4.73 (d, 1H); 4.61 (m, 1H); 7.05 (d, 2H); 7.22 (d, 2H); 7.36 (d, 2H); 7.62 (d, 2H); 7.36 (m, 1H); 7.46 (t, 2H); 7.65 (d, 2H); 8.03 (d, 1H); 11.8 (sl, H mobile)

MS

$638^+ = MH^+$; $582^+ = MH^+ - tBu + H$; $538^+ = MH^+ - CO_2tBu + H$

The following compounds (examples 3 to 25) are prepared according to the method described in examples 1 or 2 and/or according to the procedure described above. In particular, when -[A1]- represents a phenyl that may be substituted, the reaction is carried out in two steps: a) the coupling reaction is carried out with a compound of formula (III) in which A'^2 represents a hydroxyl radical and b) is used in the phosphorylation reaction. The variations known to the person skilled in the art may be used in the preparation of these active compounds. For example, the reactions of coupling amine P1 with the compound of formula (III) may also be carried out in solid phase (see examples 13, 18 and 19).

In general, the final product is purified on RP18 silica (inverse phase) in an eluent mixture CH_3CN/H_2O 50/50 + 0.1% of TFA.

EXAMPLE 3:

N-[(3S)-hexahydro-2-oxo-1-(3-phenylpropyl)-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide

R^1: -$(CH_2)_3$-phenyl; -[A^1]-: -phenyl-; A^2: OPO_3H_2 (3S)

NMR (1H, DMSO)

1.30 to 1.95 (m) 8H; 2.54 (m, 2H); 3.39 (m, 2H); 3.30 (dl) 3.60 (dd) 2H; 4.73 (dd, 1H); 7.20 to 7.30 (m, 5H); 7.24 and 7.83 (AA'BB'); 8.22 (d, NH)

MS

$MH^+ = 447^+$; $MNa^+ = 469^+$; $2MH^+ = 893^+$; $2MNa^+ = 915^+$;

$(M-H)^- = 445^-$

EXAMPLE 4:

N2-acetyl-N-[(3S)-hexahydro-1-(3-phenylpropyl)-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide

R^1: -$(CH_2)_3$-phenyl; -[A^1]-: -CH(NHAc)-CH_2-phenyl; A^2: OPO_3H_2 (3S, 2S)

MS

$MH^+ = 532^+$; $MH^+ - OPO_3H_2 = 434^+$; $MNa^+ = 554^+$; $2MH^+ = 1063^+$; $2MNa^+ = 1085^+$;

$(M-H)^- = 530^-$

EXAMPLE 5:

N-[(3S)-hexahydro-2-oxo-1-(3-phenyl-2-propenyl)-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide

R^1: -CH_2-CH = CH-phenyl; -[A^1]-: -phenyl-; A^2: OPO_3H_2 (3S)

NMR (1H, DMSO)

1.30 to 1.95 (m, 6H); 3.32 (dm) 3.62 (m) 2H; 4.07 (ddl) 4.22 (ddl) 2H; 6.20 (dt, J = 16 Hz and 6 Hz, 1H); 6.57 (dl, J = 16 Hz,

1H); 4.81 (m, 1 H); 7.24 and 7.87 (AA'BB'); 7.25 (masked, 1H); 7.33 (tl, 2H); 7.42 (dl, 2H); 8.29 (d, NH)

EXAMPLE 6:

N2-acetyl-N-[(3S)-hexahydro-1-(3-phenyl-2-propenyl)-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide

R^1: $-CH_2-CH = CH$-phenyl; $-[A^1]-$: -CH(NHAc)-CH_2-phenyl-; A^2: OPO_3H_2 (3S, 2S)

NMR (1H, DMSO)

1.30 to 1.90 (m, 6H); 2.72 (dd) 3.05 (dd) 2H; 3.28 (dm) 3.37 (ddl) 2H; 4.06 (dd) 4.22 (dd) 2H; 4.48 (m, 1H); 4.57 (ddl, 1H); 6.19 (dt, J = 16 Hz and 6 Hz, 1H); 6.57 (d, J = 16 Hz, 1H); 7.04 and 7.21 (AA'BB'); 7.24 (t, 1H); 7.32 (t, 2H); 7.43 (d, 2H); 8.00 (d, NH); 8.18 (d, NH)

EXAMPLE 7:

[[4-[(2S)-2-(acetylamino)-3-[[(3S)-1-(cyclohexylpropyl)-hexahydro-2-oxo-1H-azepin-3-yl]amino]-3-oxopropyl]phenyl]difluoromethyl]-phosphonic acid

R^1: $-(CH_2)_3$-cyclohexyl; $-[A^1]-$: -CH(NHAc)-CH_2-phenyl-; A^2: $CF_2PO_3H_2$ (3S, 2S)

MS

$570^- = [M-H]^-$

EXAMPLE 8:

N2-acetyl-N-[(3S)-1-(3-cyclohexylpropyl)-hexahydro-2-oxo-1H-azepin-3-yl]-3-(1,3-dihydro-3-hydroxy-1-oxo-5-isobenzofuranyl]-L-alaninamide

R^2: $-(CH_2)_3$-cyclohexyl; $-[A^1]-$: -CH(NHAc)-CH_2-(m-CHO)-phenyl-; A^2: $-CO_2H$ (cycled form: hydroxylactone) (3S, 2S)

MS

$514^+ = [M+H]^+$; $536^+ = [M+Na]^+$; $496^+ = MH^+ - H_2O$; $1027^+ = [2M+H]^+$; $1049^+ = 2[M+Na]^+$; $512^- = [M-H]^-$; $1025^- = [2M-H]^-$

253^+ = amine of formula I'' (caprolactam - NH)$^+$ + 2H

IR ($CDCl_3$)

Absorption region OH/NH: 3421, 3375 cm^{-1}, C = O 1769, 1660, 1631 cm^{-1}, aromatic + amide II 1490 cm^{-1} (max)

EXAMPLE 9:

N-[(3S)-hexahydro-2-oxo-1-[[4-(phenylcarbonyl)phenyl]methyl]-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide

R^1: $-CH_2$-Ph-CO-Ph; $-[A^1]-$: phenyl; A^2: OPO_3H_2 (3S)

NMR (1H, DMSO)

1.50 to 1.95 (m, 6H); 3.35 (dd, 1H) 3.67 (dd, 1H); 4.65 (d, 1H); 4.67 (d, 1H); 4.84 (m, 1H); 7.24 (d, 2H); 7.88 (d, 2H); 7.50 to 7.77 (9H aromatic); 8.35 (d, 1H NH)

MS

MH+ = 530 Da

EXAMPLE 10:

N-[(3S)-1-[[4-(cyanophenyl)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide

R^1: -CH_2-Ph-(o-CN)-Ph; -[A^1]-: -phenyl-; A^2: OPO_3H_2 (3S)

NMR (1H, DMSO)

1.55 to 2.00 (m, 6H); 3.69 (m, 2H); 4.53 (d, 1H); 4.79 (d, 1H); 4.88 (m, 1H); 7.25 (d, 2H); 7.90 (d, 2H); 7.43 (d, 2H); 7.56 (d, 2H); 7.58 (m, 1H); 7.64 (m, 1H); 7.79 (t, 1H); 7.94 (d, 1H); 9.37 (d, 1H)

MS

MNa^+ = 542 Da; MH^+ = 520 Da;

201^+ = $COPhOPO_3H_2$; 192+ = CH_2Ph-(o-CN)-Ph

EXAMPLE 11:

N-[(3s)-hexahydro-2-oxo-1-[[3,5-(trifluoromethyl)phenyl]methyl]-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide

R^1: -CH_2-(m,m'-di-CF_3)-phenyl; -[A^1]-: -phenyl-; A^2: OPO_3H_2 (3S)

NMR (1H, DMSO)

1.15 to 2.0 (m, 6H); 3.40 (dd, 1H) 3.74 (dd, 1H); 4.69 (d, 1H); 4.82 (d, 1H); 4.88 (m, 1H); 7.25 7.89 (m, H aromatic); 7.98 (s, 2H); 8.02 (s, 1H); 8.41 (d, 1H)

MS

$2MH^+$ = 1109; MH^+ = 555;

338 = MH^+ - H - $NHCOPhOPO_3H_2$; 354 = MH^+ - H - $COPhOPO_3H_2$; 201 = $COPhOPO_3H_2$

EXAMPLE 12:

2-methyl-N-[(3S)-hexahydro-2-oxo-1-(3-phenyl-2-propenyl)-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide

R^1: -CH_2-CH = CH-phenyl; -[A^1]-: -(o-Me)phenyl-; A^2: OPO_3H_2 (3S)

Rf (methanol/water 60/40) = 0.23

EXAMPLE 13:

N2-acetyl-N-[(3S)-hexahydro-1-[[3.5-(trifluoromethyl)phenyl]methyl]-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide

R^1: -CH_2-(m,m'-di-CF_3)-phenyl; -[A^1]-: -CH(NHAc)-CH^2-phenyl-; A^2: OPO_3H_2 (3S, 2S)

a) Coupling

In this case, the coupling reaction is carried out in the solid phase. 200 mg of the Wang resin HO_2C-[CH(NHAc)-CH_2-Ph-O-PO (OtBu) (OCH_2-Wang) (P2) is placed in each tube; 50 mg of the amine prepared in preparation P1, 1 ml of dichloromethane, 1 ml of HOBt in DMF and 1 ml of DCI in DMF are added, agitated overnight at ambient

temperature and washed first with DMF, then a mixture of DMF/CH_2Cl_2, then CH_2Cl_2.

b) Deprotection and deblocking

To the resin obtained above, 3 ml of TFA at 15% in CH_2Cl_2 is added. After filtration, washing and evaporation under reduced pressure, 17 mg of the product expected is obtained.

NMR (1H, DMSO)

1.00 to 2.00 (m, 6H); 2.67 (dd, 1H); 3.04 (dd, 1H); 3.35 (dd, 1H); 3.69 (dd, 1H); 4.50 (m, 1H); 4.67 (m, 1H); 4.68 (d, 1H); 4.80 (d, 1H); 7.05 (d, 2H); 7.22 (d, 2H); 7.97 (m, 2H); 8.03 (s, 1H) 8.13 (d, 1H)

MS

$MNa^+ = 662^+$; $MH^+ = 640^+$;

$355^+ = MH^+ - H - COCH(NHAc)CH_2\text{-}Ph\text{-}OPO_3H_2$

$227+ = CH_2Ph(CF_3)_2$

EXAMPLE 14:

N-[(3S)-hexahydro-2-oxo-1-[4-(1,1'-biphenyl)methyl]-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide

R^1: -CH_2-Ph-Ph; -[A^1]-: -phenyl-; A_2: OPO_3H_2 (3S)

MS

$MNa^+ = 517$ Da

$MH^+ = 495$ Da

EXAMPLE 15:

N-[(3S)-hexahydro-1-[[4-(1,1-dimethylethyl)phenyl]methyl]-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide

R^1: -CH_2-(p-tBu)phenyl; -[A^1]-: -phenyl-; A^2: OPO_3H_2 (3S)

NMR (1H, DMSO)

1.27 (s, 9H); 1.10 to 1.95 (m, 6H); 3.26 (dd, 1H); 3.60 (dd, 1H); 4.41 (d, 1H); 4.64 (d, 1H); 4.82 (m, 1H); 7.20 (d, 2H); 7.35 (d, 2H); 7.24 (d, 2H); 7.88 (d, 2H); 8.34 (d, 1H)

MS

$MH^+ = 475$

$275^+ = MH^+ - H - COPhOPO_3H_2$; $201^+ = COPhOPO_3H_2$; $147^+ = CH_2\text{-}Ph\text{-}tBu$

EXAMPLE 16:

-4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[4-(trifluoromethoxy)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino]-1-propen-1-yl] acid

R^1: -CH_2-(p-OCF_3)-phenyl; -[A^1]-: C(NHAc) = CH-(m-CHO)-phenyl-; A_2: CH_2-CO_2H (3S)

Rf (CH_2Cl_2/AcOH/MeOH: 92.5/0.8/7.5) = 0.20

EXAMPLE 17:

[4-[(2S)-2-amino-3-[[(3S)-1-(cyclohexylpropyl)-hexahydro-2-oxo-1H-azepin-3-yl]amino]-3-oxopropyl]-1,2-phenylene]bis-phosphonic acid

R^1: -$(CH_2)_3$-cyclohexyl; -[A^1]-: -CH(NH_2)-CH_2-(m-PO_3H_2)-phenyl-; A^2: -PO_3H_2 (3S, 2S)

NMR (DMSO)

0.84 to 1.82 (m, 2H); 2.33 to 4.54 (m, 8H); 7.23 (m, 1H); 7.63 (m, 1H); 7.76 (m, 1H); 8.70 (m, 1H)

MS

ES positive mode: $MH^+ = 560^+$

ES negative mode: $[M-H]^- = 558^-$

EXAMPLE 18:

N2-acetyl-N-[(3s)-hexahydro-1-[[4-(phenylcarbonyl)phenyl]methyl]-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide

R^1: -CH_2-Ph-CO-Ph; -[A^1]-: -CH(NHAc)-CH_2-phenyl-; A^2: OPO_3H_2 (3S, 2S)

The procedure is as in example 13 (coupling in solid phase) to obtain 9 mg of the expected product.

NMR (1H, DMSO)

1.10 to 1.85 (m, 6H); 1.77 (s, 3H, NHAc); 2.71 (dd, 1H); 3.03 (dd, 1H); 3.30 (dd, 1H); 3.63 (dd, 1H); 4.45 to 4.70 (m, 4H); 7.05 (d, 2H); 7.23 (d, 2H); 7.50 to 7.75 (9H); 8.07 (d, 1H); 8.17 (d, 1H)

MS

ES positive mode: $MH^+ = 608$

ES negative mode: $[M-H]^- = 606^-$

EXAMPLE 19:

N2-acetyl-N-[(3S)-1-[[4-(2-cyanophenyl)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide

R^1: -CH_2-Ph-(o-CN)-Ph; -[A^1]-: -CH(NHAc)-CH_2-phenyl-; A^2: OPO_3H_2 (3S, 2S)

The procedure is as in example 13 (coupling in solid phase) to obtain the expected product.

NMR (1H, DMSO)

1.23 (m, 1H); 1.67 (m, 1H); 1.45 (m, 1H); 1.83 (m, 1H);
1.69 (m, 1H); 1.84 (m, 1H); 1.77 (s, 3H); 2.72 (m, 1H);
3.08 (m, 1H); 4.90 (m, 1H); 3.30 (dl, 1H); 3.64 (tl, 1H);
4.64 (t, 1H); 4.52 (d, 1H); 4.78 (d, 1H); 7.06 (d, 2H);
7.24 (d, 2H); 7.42 (d, 2H); 7.55 (d, 2H); 7.62 (d, 1H);
7.79 (t, 1H); 7.58 (t, 1H); 7.95 (d, 1H); 8.08 (d, 1H);
8.17 (d, 1H).

MS

MH^+ = 605 Da

EXAMPLE 20:

4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[(1,1'-biphenyl)-4-yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino] 1-propen-1-yl]-2-formyl-benzeneacetic acid

R^1: -CH_2-Ph-Ph; -[A^1]-: -C(NHAc) = CH-(m-CHO)-phenyl-; A^2: CH_2-CO_2H (3S)

Rf (CH_2Cl_2/AcOH/MeOH: 92.5/0.8/7.5) = 0.19

EXAMPLE 21:

4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[(1,1'-biphenyl)-4-yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino] 1-propen-1-yl]-alpha-fluoro-2-formyl-benzeneacetic acid

R^1: -CH_2-Ph-Ph; -[A^1]-: -C(NHAc) = CH-(m-CHO)-phenyl-; A^2: CHF-CO_2H (3S)

Rf (CH_2Cl_2/AcOH/MeOH: 87.5/3.0/12.5) = 0.13

EXAMPLE 22:

4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[1,1'-biphenyl)-4-yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino] 1-propen-1-yl]-2-[(aminocarbonyl)hydrazono]-alpha-fluoro-benzeneacetic acid

R^1: -CH_2-Ph-Ph; -[A^1]-: -C(NHAc) = CH-(m-CH = N-$NHCONH_2$)-phenyl-; A^2: CHF-CO_2H (3S)

Rf (CH_2Cl_2 / MeOH: 60/40) = 0.28

EXAMPLE 23:

4-[3-[[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-azepin-3-yl]amino]-(2S)-2(acetylamino)-3-oxo-1-propyl-]-2-formyl-benzoic acid

(2R)-2-(acetylamino)-3-oxo-1-propyl-]-2-formyl-benzoic

R^1: -CH_2-Ph-Ph; -[A^1]-: -C(NHAc)-CH_2-(m-CHO)phenyl-; A^2: CO_2Me (3S, 2S)

MS

$570^+ = [M+H]^+$; $592^+ = [M + Na]^+$; $1161^+ = [2M + Na]^+$

EXAMPLE 24:

N2-acetyl-N-[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-3-(1,3-dihydro-3-hydroxy-1-oxo-5-isobenzofuranyl]-L-alaninamide

R^1: -CH_2-Ph-Ph; -[A^1]-: -C(NHAc)-CH_2-phenyl-; A^2 and R^2 together form a group: -CH(OH)-O-C(O)- (3S, 2S)

1.3 ml of soda 2N is added to a solution of 120 mg methyl ester described in Example 23 in 6 ml of THF, agitated at ambient temperature for 1 hour 30 minutes, acidified using chlorhydric acid 1N at pH 1, absorbed with ethyl acetate, decanted, washed, dried and evaporated under reduced pressure until 110 mg of the gross product is obtained, which is purified using chromatography with the mixture CH_2Cl_2/MeOH 90/10 as the eluent. Absorption with ether and 55 mg of the expected purified product is obtained.

MS

578 Da = MNa^+; 556 Da = MH^+; 538 Da = $MH^+ - H_2O$

EXAMPLE 25:

[[4-[(2S)-2-(acetylamino)-3-[[(3S)-1-[[(1,1'-biphenyl)yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino]3-oxo-1-propyl]-phenyl]difluoromethyl]-phosphonic acid

R^1: $-CH_2$-Ph-Ph; -[A^1]-: -C(NHAc)-CH_2-phenyl-; A^2: $CF_2PO_3H_2$ (3S, 2S)

NMR (1H, DMSO)

1.18 (m, 1H); 1.44 (m, 1H); 1.68 (m, 2H); 1.84 (m, 2H); 1.78 (s, 3H); 2.81 (dd, 1H); 3.15 (dd, 1H); 3.29 (dd, 1H); 3.58 (dd, 1H); 4.44 - 4.82 (m, 3H, system AB); 7.31 - 7.63 (AA'BB'); 8.14 and 8.24 (NH).

The following compounds have also been prepared:

- 4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[(1,1'-biphenyl)-4-yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino] 1-propen-1-yl]-2-(methoxycarbonyl)-propane dioate bis (1,1-dimethylethyl),

- 4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[4-(trifluoromethoxy)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3)-yl]amino]-1-propen-1-yl]-2-(methoxycarbonyl)-benzene- acetic acid,

- 4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[4-(trifluoromethoxy)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino]1-propen-1-yl]-2-(methoxycarbonyl)-benzeneacetic acid ammonium salt,

- [4-[(2S)-2-(acetylamino)-3-[[(3S)-1-(cyclohexylpropyl)-hexahydro-2-oxo-1H-azepin-3-yl]amino]-3-oxopropyl]-1,2-phenylene]-bis-phosphonic acid,

-[(2S)-1-[[(3S)-hexahydro-1-[[(4-phenoxyphenyl)amino]-2-oxoethyl]-2-oxo-1H-azepin-3-yl]amino]-1-oxo-3-[4-(phosphonooxy)phenyl)propyl]-carbamate 1,1-dimethylethyl,

- N2-acetyl-N-[(3S)-1-[[4-(1,1-dimethylethyl)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide.

Pharmacological study of the products according to the invention

Measurement of the IC50 by scintillation proximity assay (SPA)

The capacity of the molecules to connect to the Src-SH2 protein is evaluated by competition (measurement of the IC_{50}) in a test called scintillation proximity assay (SPA). This test uses PVT balls (Amersham) which contain the scintillant. These balls coated with Streptavidin are incubated in an MOPS buffer in 9-plates, then with 50 nM of SH2 protein that was previously biotinylated, then with the ligand EPQpYEEIPIYL labeled with iodine 125. In connecting to the protein fixed on the ball, the ligand activates the scintillant, which emits light measured in a Wallac micro_eta scintillation computer. The value obtained in the absence of any competitor corresponds to the

maximum bonding of the ligand on the protein. This method does not require separating the free ligand from the bond.

The molecules to be tested are diluted in the MOPS buffer containing 2% DMSO and added at different concentrations from 0.1 nM to 100 µM in wells containing the ligand before the addition of the balls coated with Src-SH2. After 1 hour of incubation, a measurement of the bond is carried out using a scintillation counter. Inhibition of the radiolabeled ligand bond by the different concentrations of competitor make it possible to evaluate the IC50 of the molecules tested.

Result

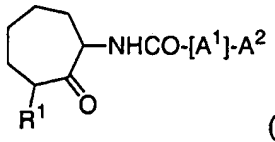
SPA results: Reference peptide

PYEEI _ 0.2 - 0.4 µmol

EXAMPLE no.	IC_{50} (µMol)
1	0.009
2	0.046
3	4.5
4	0.29
5	2.26
6	0.28
7	0.34
8	0.57
9	3.0
10	2.1
12	2.5
13	2.2
14	1.6
15	2.4
16	5
18	0.36
19	0.026
20	2.20
21	2.04
24	0.120
25	0.005

CLAIMS

1) A compound of formula (I):



(I)

in which,

$-R^1$ is

either R'^1, representing the following groups:

$(C_1\text{-}C_8)$-alkyl-, $(C_2\text{-}C_8)$-alkenyl-, $(C_2\text{-}C_8)$-alkynyl-, $(C_5\text{-}C_{14})$-aryl-$(C_1\text{-}C_8)$-alkyl-, $(C_5\text{-}C_{14})$-aryl-$(C_2\text{-}C_8)$-alkenyl-, $(C_5\text{-}C_{14})$-aryl-$(C_2\text{-}C_8)$-alkynyl-, $(C_3\text{-}C_{18})$-cycloalkyl-$(C_1\text{-}C_8)$-alkyl-, $(C_3\text{-}C_{18})$-cycloalkyl-$(C_2\text{-}C_8)$-alkenyl-, $(C_3\text{-}C_{18})$-cycloalkyl-$(C_2\text{-}C_8)$-alkynyl- or $(C_5\text{-}C_{14})$-aryl-, the said alkyl, alkenyl, alkynyl, aryl and cycloalkyl groups being non-substituted or substituted by one or several R^2 radicals,

or R''^1, representing the following groups:

$-CHRa\text{-}CO\text{-}R'^1$, $-CHRa\text{-}CONH\text{-}R'^1$, R'^1 being as defined above;

- $-[A^1]-$ representing a group chosen from among:

$-CH(Z)\text{-}(C_1\text{-}C_4)\text{-alkyl-}(C_5\text{-}C_{14})\text{-aryl-}$, $-C(Z)=CH\text{-}(C_0\text{-}C_2)\text{-alkyl-}(C_5\text{-}C_{14})\text{-aryl-}$, $-CH(Z)\text{-}(C_5\text{-}C_{14})\text{-aryl-}$, $-(C_1\text{-}C_4)\text{-alkyl-}(C_5\text{-}C_{14})\text{-aryl-}$ and $-(C_5\text{-}C_{14})\text{-aryl-}$,

in which Z is an atom of hydrogen, a tetrazol, NRbRc, NHCORb, CONHRb, $NHCO_2Rb$, $NHCOCO_2Rb$, NHSORb or $NHSO_2Rb$; the said aryl radicals being substituted or non-substituted by R^2 or R'^2;

- A_2 represents a group chosen from among

-PO (ORd) (ORe), -OPO (ORd) (ORe), -B (ORd) (ORe),

$-CRfRgPO$ (ORd) (ORe), -O-CRfRgPO (ORd) (ORe), $-CRfRg\text{-}CO_2Rd$,

$-CRfRg\text{-}CO_2Rd$, $-CRfRg\text{-}CH_2\text{-}CO_2Rd$, $-CRfRgSO_3H$, $-CO_2Rd$,

$-CH\ (CH_2CO_2Rd)\ (CH_2CO_2Re)$, -NHCO-PO (ORd) (ORe), and

-CO-PO (ORd) (ORe);

- Ra, Rb, Rc, Rd or Re, independent of each other, identical or different, represent an atom of hydrogen, a $(C_1\text{-}C_8)$-alkyl, $(C_3\text{-}C_{18})$-cycloalkyl, $(C_3\text{-}C_{18})$-(cycloalkyl)-$(C_1\text{-}C_8)$-alkyl-, $(C_5\text{-}C_{14})$-aryl- or $(C_5\text{-}C_{14})$-aryl-$(C_1\text{-}C_4)$-alkyl- radical, the said radicals being substituted or non-substituted by one or several R^2 radicals;

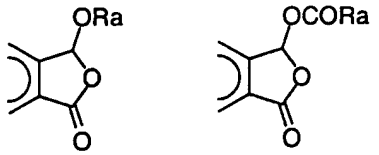
- Rf and Rg, identical or different, represent an atom of hydrogen, a halogen, a CO_2Rd, SO_3Rd, ORd, NHRd, PO (ORd) (ORe) radical or tetrazol;

- R^2 represents a $(C_1\text{-}C_8)$-alkyl-, $(C_1\text{-}C_8)$-alkoxy-, $(C_1\text{-}C_3)$-alkylenedioxy-, $(C_5\text{-}C_{14})$-aryl-, $(C_5\text{-}C_{14})$-aryloxy-, $(C_5\text{-}C_{14})$-aryl-$(C_1\text{-}C_4)$-alkyl-, $(C_5\text{-}C_{14})$-aryl-$(C_1\text{-}C_4)$-alkyloxy-, halogen, trihalogenomethyl-, trihalogenomethyloxy-, hydroxyl, nitro, formyl,

-C=NH-NH-CO-NH_2, cyano, carboxy, -$CONH_2$, (C_1-C_8)-alkyloxycarbonyl-, amino, -NH-((C_1-C_4)-alkyl), -N((C_1-C_4)-alkyl)$_2$, -NHCO-(C_1-C_4)-alkyl, -NHCO-(C_5-C_{14})-aryl, -CONH-(C_1-C_4)-alkyl, -CONH-(C_5-C_{14})-aryl, -CO-(C_1-C_4)-alkyl or -CO-(C_5-C_{14})-aryl group;

- R'^2 has the same values as A^2;

- If necessary, A^2 and R^2 form, together with the phenyl that they have, one of the cycles with 5 bonds as follows:



the said compounds of formula (I) being of all their possible isomer forms, alone or in mixtures of any ratio whatsoever, as well as their physiologically acceptable salts and their prodrugs.

2) Isolated enantiomer or diastereoisomer of formula (I) according to claim 1, characterized in that the carbon in position 3 which holds the -NHCO-[A^1]-A^2 group presents the S configuration.

3) Diastereoisomer of formula (I) according to claim 1 or 2, characterized in that the carbon in position 3 which holds the -NHCO-[A^1]-A^2 group presents the S configuration and the carbon that has the -Z group such as defined in claim 1, with the exception of hydrogen, presents the S configuration.

4) Compounds of formula (I) according to any one of claims 1 to 3 in which R^1 is a radical R'^1 as defined in claim 1.

5) Compounds of formula (I) according to any one of claims 1 to 4 in which R^1 is a radical, phenyl-(C_1-C_8)-alkyl-, phenyl-(C_2-C_8)-alkenyl-, phenyl-(C_2-C_8)-alkynyl-, cyclohexyl-(C_1-C_8)-alkyl-, cyclohexyl-(C_2-C_8)-alkenyl-, cyclohexyl-(C_2-C_8)-alkynyl-, the said aryls being substituted or non-substituted by one or several R^2 radicals.

6) Compounds of formula (I) according to any one of claims 1 to 4 in which -[A^1]- represents a group chosen from among -CH(Z)-(C_1-C_4)-alkyl-phenyl-, -phenyl-, -C(Z) = CH-phenyl-, -C(Z) = CH-naphtyl-, -indolyl-, -CH_2-phenyl-, -CH_2-pyridinyl-, the said phenyl, naphthyl, indolyl or pyridinyl radicals being substituted or not substituted by R^2 or R'^2.

7) Compounds of formula (I) according to claims 6 in which, when -[A_1]- includes a phenyl group substituted by R^2 or R'^2, R^2 is preferably a -CHO or (C_1-C_4)-alkyloxy-, -carbonyl- group and R'^2 is preferably an -OPO_3H_2 or PO_3H_2 group, R^2 and R'^2 especially being in the meta position when A^2 is in the para position.

8) Compounds of formula (I) according to any one of claims 1 to 4 in which -A^2 preferably represents -PO (OH) (OH), -OPO (OH) (OH), -CR'fR'gPO (OH) (OH), -O-

CR'fR'gPO (OH) (OH); -O-CR'f (CO_2H)2, -CR'fR'g-CO_2H, -CR'fR'g-CH_2-CO_2H, -CH (CH_2CO_2H) (CH_2CO_2H), -CO_2H or -NHCO- PO (OH) (OH), R'f and R'g, identical or different, representing a halogen atom, especially fluorine or a hydrogen atom and A^2 is most preferably in para position.

9) Compounds of formula (I) according to any one of claims 1 to 4 in which Z represents NHCORc, $NHCO_2Rc$, in which Rc represents an alkyl radical containing 1 to 6 carbon atoms.

10) A compound of formula (I) such as is described in any one of claims 1 to 10 in which R^1 is a phenyl-(C_1-C_8)-alkyl-, phenyl-(C_2-C_8)-alkenyl-, phenyl-(C_2-C_8)-alkynyl-, cyclohexyl-(C_1-C_8)-alkyl, cyclohexyl-(C_2-C_8)-alkenyl-, cyclohexyl-(C_2-C_8)-alkynyl- radical, the said aryls being substituted or non-substituted by one or more R^2 radicals,

- [A_1]- represents a group chosen from among -CH(Z)-(C_1-C_4)-alkyl-phenyl-, -phenyl, -C(Z) = CH-phenyl-, -C(Z) = CH-naphthyl-, -indolyl-, -CH_2-phenyl-, -CH_2-pyridinyl-, the said phenyl, naphthyl, indolyl or pyridinyl radicals being substituted or not substituted by R^2 or R'^2,

- A^2 preferably represents -O-PO_3H_2, -CF_2-PO_3H_2, -CH_2CO_2H, $CHFCO_2H$ or CF_2CO_2H,

- Z represents NHCORc, $NHCO_2Rc$, in which Rc represents an alkyl radical containing 1 to 6 carbon atoms,

the said compounds of formula (I) being in all their possible isomer forms, alone or in mixture in any ratio whatsoever, as well as their physiologically acceptable salts and their prodrugs.

11) The compounds of formula (I) with the following names:

. N2-acetyl-N-[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide,

. [(2S)-1-[[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino]-1-oxo-3-[4-(phosphonoxy)phenyl]propyl]-carbamate 1,1-dimethylethyl,

. N-[(3S)-hexahydro-2-oxo-1-(3-phenylpropyl)-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide,

. N2-acetyl-N-[(3S)-hexahydro-1-(3-phenyl-2-proprenyl)-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide,

. N-[(3S)-hexahydro-2-oxo-1-(3-phenyl-2-propenyl)-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide,

. N2-acetyl-N-[(3S)-hexahydro-1-(3-phenyl-2-propenyl)-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide,

. [[4-[(2S)-2-(acetylamino)-3-[[(3S)-1-(cyclohexylpropyl)-hexahydro-2-oxo-1H-azepin-3-yl]amino]-3-oxopropyl]phenyl]difluoromethyl]-phosphonic acid,

. N2-acetyl-N-[(3S)-1-(3-cyclohexylpropyl)-hexahydro-2-oxo-1H-azepin-3-yl]-3-(1,3-dihydro-3-hydroxy-1-oxo-5-isobenzofuranyl]-L-alaninamide,

. N-[(3S)-hexahydro-2-oxo-1-[[4-(phenylcarbonyl)phenyl]methyl]-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide,

. N-[(3S)-1-[[4-(cyanophenyl)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide,

. N-[(3s)-hexahydro-2-oxo-1-[[3,5-(trifluoromethyl)phenyl]methyl]-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide,

. 2-methyl-N-[(3S)-hexahydro-2-oxo-1-(3-phenyl-2-propenyl)-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide,

. N2-acetyl-N-[(3S)-hexahydro-1-[[3.5-(trifluoromethyl)phenyl]methyl]-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide,

. N-[(3S)-hexahydro-2-oxo-1-[4-(1,1'-biphenyl)methyl]-1H-azepin-3-yl]-4-(phosphonooxy)-benzamide,

. -4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[4-(trifluoromethoxy)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino]-1-propen-1-yl] acid,

. [4-[(2S)-2-amino-3-[[(3S)-1-(cyclohexylpropyl)-hexahydro-2-oxo-1H-azepin-3-yl]amino]-3-oxopropyl]-1,2-phenylene]bis-phosphonic acid,

. N2-acetyl-N-[(3S)-hexahydro-1-[[4-(phenylcarbonyl)phenyl]methyl]-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide,

. N2-acetyl-N-[(3S)-1-[[4-(2-cyanophenyl)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide,

. 4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[(1,1'-biphenyl)-4-yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino] 1-propen-1-yl]-2-formyl-benzeneacetic acid,

. 4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[(1,1'-biphenyl)-4-yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino] 1-propen-1-yl]-alpha-fluoro-2-formyl-benzeneacetic acid,

. 4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[1,1'-biphenyl)-4-yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino] 1-propen-1-yl]-2-[(aminocarbonyl)hydrazono]-alpha-fluoro-benzeneacetic acid,

. 4-[3-[[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-azepin-3-yl]amino]-1-propen-1-yl]-2-[(aminocarbonyl)hydrazono]-alpha-fluoro-benzeneacetic acid,

. 4-[3-[[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-azepin-3-yl]amino]-(2S)-2(acetylamino)-3-oxo-1-propyl-]-2-formyl-benzoic acid,

. N2-acetyl-N-[(3S)-1-[4-(1,1'-biphenyl)methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-3-(1,3-dihydro-3-hydroxy-1-oxo-5-isobenzofuranyl]-L-alaninamide,

. [[4-[(2S)-2-(acetylamino)-3-[[(3S)-1-[[(1,1'-biphenyl)yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino]3-oxo-1-propyl]-phenyl]difluoromethyl]-phosphonic acid,

- 4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[(1,1'-biphenyl)-4-yl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino] 1-propen-1-yl]-2-(methoxycarbonyl)-propane dioate bis (1,1-dimethylethyl),

- 4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[4-(trifluoromethoxy)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3)-yl]amino]-1-propen-1-yl]-2-(methoxycarbonyl)-benzene- acetic acid,

- 4-[2-(acetylamino)-3-oxo-3-[[(3S)-1-[[4-(trifluoromethoxy)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]amino]1-propen-1-yl]-2-(methoxycarbonyl)-benzeneacetic acid ammonium salt,

- [4-[(2S)-2-(acetylamino)-3-[[(3S)-1-(cyclohexylpropyl)-hexahydro-2-oxo-1H-azepin-3-yl]amino]-3-oxopropyl]-1,2-phenylene]-bis-phosphonic acid,

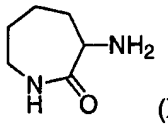
- [(2S)-1-[[(3S)-hexahydro-1-[[(4-phenoxyphenyl)amino]-2-oxoethyl]-2-oxo-1H-azepin-3-yl]amino]-1-oxo-3-[4-(phosphonooxy)phenyl)propyl]-carbamate 1,1-dimethylethyl,

- N2-acetyl-N-[(3S)-1-[[4-(1,1-dimethylethyl)phenyl]methyl]-hexahydro-2-oxo-1H-azepin-3-yl]-4-(phosphonooxy)-L-phenylalaninamide,

as well as their physiologically acceptable salts and their prodrugs.

12) A preparation procedure for compounds of formula (I) such as defined in any one of claims 1 to 11, which includes coupling or two or more fragments which may be derived by retrosynthesis from the compounds of formula (I).

13) A procedure according to claim 12 in which the preparation of the compounds of formula (I) is carried out by coupling an amine of the formula (II)



(II)

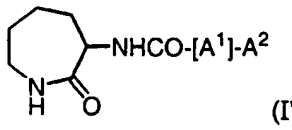
where, if necessary, the functional group is in the form of the precursor or in protected form,

with

a) either at first with an acid or an acid derivative of the formula (III)

$$X\text{-}C(=O) - [A^1] - A'^2 \qquad \text{(III)}$$

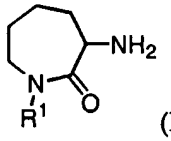
in which $[A^1]$ is as defined above in the formula (I) and A'^2 representing, in addition to the values of A^2, the hydroxy radical, X is a group that can be substituted by a nucleophile or where, if necessary, the functional groups are in the form of precursors or in the protected form, in order to obtain a compound of the formula (I')



(I')

then R^1-X' is allowed to react, R^1 being as defined above and X' preferably being an iodine, a bromine or a mesylate group; the said functional groups possibly present in the form of precursor or in the protected form being then converted into groups present in the compounds of formula (I);

b) or at first with R^1-X', in order to obtain, after deprotection if necessary, the compound of the formula (I")



(I")

then with acid or the acid derivative of formula (III), the said functional groups possibly present in the form of the precursor or in the protected form, being then converted into groups present in the compounds of formula (I). If desired or if necessary, certain compounds of formula (I) may be subjected to one or more of the following reactions in an appropriate order:

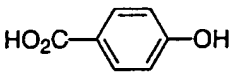
- Action of a monodebenzylation agent when [A'2] represents OPO $(OBn)_2$,
- Action of a total deprotection agent,
- Action of H-P (O) (ORd) (ORe) when A'2 represents OH,
- Obtaining different values of Z (NHCORc, NHSORc, $NHCO_2Rc$, $NHSO_2Rc$) starting with the corresponding amine (Z = NH_2),
- Saponification, then decarboxylation of the malonic derivative,
- Reduction of the double bond when -[A1]- represents a -C (Z) = CH-(C_0-C_2)-alkyl-(C_5-C_{14})-aryl group,
- Separation of the enantiomers or the diastereoisomers,
- Salification.

14) Procedure according to claim 13 in which the compound of formula (III) is chosen from among the following phosphated tyrosines:

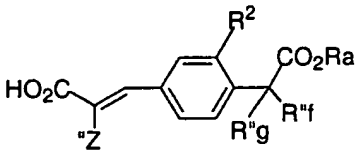
N-Boc-Tyr-O-(PO_3Bn_2), N-Ac-Tyr-O-(PO_3Bn_2),

N-Boc-Tyr-CF_2-(PO_3Et_2), N-Ac-Tyr-CF_2- (PO_3Et_2)

or the benzoic derivatives (IIIa) or benzenic derivatives (IIIb)



(IIIa)



(IIIb)

in which R"f represents an atom of hydrogen, fluorine or CO_2Rd, R"g represents an atom of hydrogen or fluorine and Z" represents NHCORb or $NHCO_2Rb$, the compound of formula (IIIb) presenting an E or Z configuration, Ra, Rb and Rd being as defined in claim 1.

15) As a medication, a compound of formula (I) and/or its physiologically acceptable salts and/or its prodrugs such as defined in any one of claims 1 to 11.

16) A pharmaceutical compound containing at least one compound of formula (I) as defined in any one of claims 1 to 11 and/or its physiologically acceptable salts and/or its prodrugs and one or more inert pharmaceutical agents and/or one or more of the usual additives.

17) As a medication having an antagonist activity to the SRC SH2 receptor, a compound of formula (I) and/or its physiologically acceptable salts and/or its prodrugs as defined in any one of claims 1 to 11.

18) As a medication having an activity that inhibits bone resorption or for the treatment or prevention of osteoporosis, a compound of formula (I) and/or its physiologically acceptable salts and/or its prodrugs as defined in any one of claims 1 to 11.

19) As a medication for treatment or prevention of immunity, infection, allergy and autoimmune diseases, a compound of formula (I) and/or its physiologically acceptable salts and/or its prodrugs as defined in any one of claims 1 to 11.

20) As a medication for treatment or prevention of diseases such as proliferative diseases, cancer, restenosis, inflammation, allergies or cardiovascular diseases, a compound of formula (I) and/or its physiologically acceptable salts and/or its prodrugs as defined in any one of claims 1 to 11.

21) Use of the compounds of formula (I) and/or their physiologically acceptable salts and/or their prodrugs as defined in any one of claims 1 to 11 for preparation of medications intended to prevent or treat osteoporosis.

22) Use of the compounds of formula (I) and/or their physiologically acceptable salts and/or their prodrugs as defined in any one of claims 1 to 11 for preparation of medications intended to prevent or treat immunity, infection, allergy and autoimmune diseases.

23) Use of the compounds of formula (I) and/or their physiologically acceptable salts and/or their prodrugs as defined in any one of claims 1 to 11 for preparation of medications intended to prevent or treat diseases such as proliferative diseases, cancer, restenosis, inflammation, allergies or cardiovascular diseases.

24) Intermediates of formulas (IIIb), (I') or (I") such as defined in claims 13 or 14.